VOLUME LXX

NUMBER 2

Hospital Library

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

February, 1942

The Present Incidence of Tuberculous Infection. WILLIAM H. CARNES 101

A Clinical and Anatomical Study of Neurological Conditions Resulting from Metastases in the Central Nervous System Due to Carcinoma of the Lung. ARTHUR B. KING AND FRANK R. FORD 124

Dietary Protein and the Regeneration of Serum Albumin. IV. The Potency Values of Dried Beef Serum, Whole Egg, Cow's Milk, Cow's Colostrum, Lactalbumin, and Wheat Gluten. A. A. WEECH 157

Nutritional Dermatoses in the Rat. VII. Notes on the Posture, Gait and Hypertonicity Resulting from a Diet Containing Unheated, Dried Egg White as the Source of Protein. MAURICE SULLIVAN, M.D., LAWRENCE KOLB, M.D., AND JANE NICHOLLS, M.Sc. 177

Proceedings of the Meeting of the Johns Hopkins Medical Society 187

Book Reviews 193

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore, Maryland

Made in United States of America

COPYRIGHT, 1942, BY THE JOHNS HOPKINS PRESS

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, JAMES BORDLEY, III

EDITORIAL BOARD

E. Cowles Andrus — Chalmers L. Gemmill
Charles R. Austrian — L. Emmett Holt, Jr.
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.85 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefor adjusted accordingly.

Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

THE PRESENT INCIDENCE OF TUBERCULOUS INFECTION

WILLIAM H. CARNES

From the Departments of Pathology, The Johns Hopkins University School of Medicine, the Baltimore City Hospitals, and the College of Physicians and Surgeons, Columbia University

Submitted for publication December 9, 1941

The very great prevalence of tuberculous infection in urban communities was first indicated by the classical study of Naegeli (1) in which a thorough search of the viscera at postmortem examination was made for small and obscure lesions which would frequently be missed in the ordinary routine autopsy. As a result of this search evidence of past tuberculous infection was found in virtually every adult in a series examined at autopsy in the Pathological Institute of Zurich in 1897 and 1898. Corroborative results were soon reported by Burkhardt in Dresden (2) and somewhat later by others in Bern (3), St. Louis (4), and Freiburg (5). Only a few years after the original study the introduction of the cutaneous tuberculin test by von Pirquet greatly extended the field of investigation of the incidence of tuberculous infection. A number of surveys in various European cities soon appeared in support of the impression gained from the anatomical studies, for the great majority of children by the age of 15 years or less were found sensitive to tuberculin (6, 7, 8, 9).

Aside from their epidemiological interest these results were of great importance in the formulation of concepts regarding the pathogenesis of adult tuberculosis. A basis was afforded for the difference in the pathology of progressive tuberculosis in childhood and adult life in perfect harmony with the results of animal experimentation. One of the most striking effects resulting from previous immunization in experimental tuberculosis is the inhibition of dissemination of infection. In contrast to the massive caseation of the regional lymph nodes and the early generalization of the infection that occurs in primary infection, in the animal possessing acquired resistance as a result of a previous infection the lymph nodes draining a site of reinfection are

much less involved and generalization of the infection is greatly inhibited. This same contrast is seen between adult and childhood tuberculosis in the human being. With the conviction that virtually every adult had had a previous (immunizing) infection it became reasonable to ascribe the characteristics of the adult disease to the previous infection. This has been a prevailing concept to the present time.

It is important to realize, however, that there were not a few dissenting voices regarding the prevalence of tuberculous infection in adults from even the earliest times. During the same period when the high incidence was being established in certain cities, there were reports from others, such as Oslo (10), Berlin (11), Posen (12), Zwickau (12), Düsseldorf (12), Magdeburg (13), Chemnitz (14), and even Vienna (15), in which similarly careful postmortem anatomical searches were said to have shown far lower percentages of infected adults than the first mentioned studies. Lubarsch (12), particularly, emphasized the local differences in the prevalence of tuberculous infection. Some of the factors which might have contributed to the differences in the results of these two groups of investigators will be discussed in a later paragraph. Discrepancies of the same kind in the reported tuberculin surveys at that time are of less importance because of the lack of uniformity in the method of testing and the low sensitivity of the Pirquet test as used by many of those investigators.

In spite of the contradictory reports it is evident from the statements in textbooks discussing tuberculosis, that the doctrine of the "universality of tuberculous infection" was generally accepted in the early part of this century. Now, however, it is stated by most authors that whereas the vast majority of primary infections formerly occurred in childhood, this is no longer true, at least not in the United States. The evidence which forms the basis for this belief is the low incidence of positive reactors in many tuberculin surveys in the past decade (16) and the reinvestigations in some communities where formerly high incidences of positive reactors have now significantly changed (17, 18). It has been conceived that the sharp decline in mortality and morbidity from the disease, which has characterized the modern era, has so reduced the number of infective cases as greatly

to lower the rate of exposure, even to the point where many individuals may never be exposed.

Such a change in the incidence of infection would have both practical and theoretical importance. However, there are certain objections to accepting this as a fact purely on the basis of the tuberculin surveys. In the first place these surveys have tested mostly children and students in colleges and professional schools. They have thus not been truly representative of the community in either age or class. Furthermore, a diminished proportion of positive reactors to tuberculin in a community has not constituted an altogether satisfactory evidence for a decreased incidence of infection. Rich (16) in discussing this evidence has recalled the numerous demonstrations that in the experimental animal hypersensitivity wanes following a well resisted infection unless it is reanimated by subsequent fresh infections, and he has pointed out that the marked reduction in the number of open cases of tuberculosis in the population today may have reduced the exposure rate sufficiently to allow many infected individuals to lose their hypersensitivity by escaping the hypersensitivity-reanimating influence of reinfections. In support of this possibility it was pointed out that numerous recent observers have found that an appreciable number of tuberculin-negative individuals show evidence of healed tuberculous lesions by X-ray (19, 20, 21, 22, 23) and that others (24, 25, 26, 27) have followed the transition from a positive to a negative reaction in a surprisingly large percentage of individuals studied. It may be significant that recent reports from several localities have shown that the percentage of individuals who have been observed to become tuberculin negative after having been tuberculin positive (28, 29) or who are tuberculin negative though possessing healed lesions demonstrable by X-ray[1] (22, 23, 30, 31) is very much higher than in the studies in former times.

It is evident that the value of tuberculin surveys in determining the incidence of infection under the conditions prevailing today is subject to doubt. More certain information must be gotten by the original

[1] Although the extremely high incidence of intrathoracic calcified lesions in some of these localities has raised a question as to their etiology (32), this has not yet been proven to be other than tuberculous.

method of postmortem anatomical search. This is the report of such a study which was undertaken in Baltimore at the suggestion of Dr. Arnold R. Rich.

MATERIAL AND METHOD

This survey comprises a representative sample of 536 cases of the autopsied deaths at the Baltimore City Hospitals from March to July, 1938, and at the Johns Hopkins Hospital, from July, 1938 through December, 1940. It is composed largely of residents of the city of Baltimore of the lower income groups, although all economic classes are represented in the Johns Hopkins Hospital series through the inclusion of private and semi-private cases as well. The patients were of all ages from the arbitrary lower limit of 6 weeks to 89 years. In an effort to balance the different age groups as nearly equally as possible, only cases under 40 years of age were included during the last year of the study. All cases in which tuberculosis was the major cause of death were excluded from the series. Only those cases were included in which a complete examination of the lungs, together with all the tracheal and bronchial lymph nodes, was possible. No other basis of selection was used.

The technique of the examination was essentially the same as that first employed by Opie (4) in a similar survey in 1916. Either before or after fixation in Kaiserling's Solution I, the entire lungs, together with the tracheal and bronchial lymph nodes, and as many of the cervical nodes as could be obtained, were X-rayed. The specimens were later examined with the X-ray plate as a guide. All shadows were identified and examined grossly. This method quickly disclosed most of the caseous and partially calcified lesions as well as the stony hard ones. Calcified lesions no more than 1–2 mm. in diameter were clearly shown. Even fibrous scars were frequently identified in the X-ray film. When no suspicious lesions were disclosed by the film, they were carefully sought by slicing all the bronchial and tracheal lymph nodes, as well as the lung parenchyma, into thin slices after hardening in the Kaiserling's solution. When there was uncertainty regarding the tuberculous nature of a lesion after gross examination, it was taken for histological study. It was also customary to make histological sections of numerous tracheobronchial lymph nodes in those cases where no suspicious lesions were found grossly.

The mesenteries of 153 cases were likewise X-rayed although experience showed that calcified mesenteric lesions were seldom missed by gross examination without the use of the X-ray. The above procedure was used as a supplement to the routine postmortem examination. All the viscera of these cases were also subjected to the usual thorough gross and microscopical examinations and the results of this study in uncovering latent tuberculous lesions were added to those of the special search already described.

The criteria used for the diagnosis of a healed, isolated tuberculous lesion require only slight elaboration. Sharply circumscribed, calcified nodules within the

parenchyma of the lung or in the lymph nodes were considered tuberculous when surrounded by a perfectly definite fibrous capsule. They are usually smoothly rounded in contour but this is not an essential characteristic and is particularly inconstant in the lymph nodes. Confusion is most likely to arise between tiny healed tuberculous lesions in the parenchyma of the lung, and phleboliths or isolated fragments of metaplastic bone. The close association of phleboliths with a small vein is usually obvious and the venous elastic pattern is found preserved in the surrounding vessel wall microscopically. The fragments of metaplastic bone are usually easy to distinguish grossly by their fuzzy surface and the lack of a fibrous capsule. Both of these lesions are rather uncommon. Although healed lesions of Coccidioidal granuloma are said to be grossly indistinguishable from the healed Ghon complex of tuberculosis (33), this infection is rare in this locality and the fungi have never been discovered in sections of numerous lesions made during the course of this study.

Fibrous scars offer the greatest difficulty in diagnosis. These are especially common at the apices of the lungs contiguous with the pleura. The etiology of these apical scars has been the subject of much controversy. It was therefore always the practice in this study to make several histological sections of each scar of this kind when other gross evidence of tuberculosis was lacking. In accordance with the custom of only accepting specific lesions as evidence of tuberculosis, these scars were not classified as positive when microscopic search failed to reveal typical tubercles or calcified lesions.

RESULTS

The observed incidence of infected individuals in each of the several age groups is shown in Table 1. The white and negro cases are listed separately in the first two columns. There are large differences in the percentage of positives between the white and negro cases in several age groups. However, owing to the small numbers of individuals involved, the differences between the races cannot be considered significant in any age group.[2] Moreover, there is no consistency in the direction of the deviations between the races. For these reasons the two have been combined in the third column of the table. A similar comparison of the male and female cases has revealed no significant difference in their percentages of infection.

In the last column of Table 1 the values of the standard deviation for each percentage of the total column are listed. The large values in certain age groups render the observed percentages of very little use. For this reason the curve (Fig. 1) has been drawn to indicate

[2] Each pair of percentages was submitted to the chi square test (29).

TABLE 1

The incidence of positively identifiable tuberculous lesions in 536 autopsies

AGE	WHITE			NEGRO			TOTAL			
	Number cases	Number positive	Per cent positive	Number cases	Number positive	Per cent positive	Number cases	Number positive	Per cent positive	S.D.*
years										
Under 1	24	1	4.2	26	0	0	50	1	2.0	2.0
1–4	22	1	4.6	20	1	5.0	42	2	4.8	3.3
5–9	10	3	30.0	12	1	8.3	22	4	18.2	8.2
10–14	5	2	40.0	3	2	66.7	8	4	50.0	17.7
15–19	14	7	50.0	10	6	60.0	24	15	54.2	10.1
20–24	17	14	82.4	10	7	70.0	27	21	77.8	8.0
25–29	20	18	90.0	17	13	76.5	37	31	83.8	6.1
30–34	19	15	79.0	26	20	76.9	45	35	77.7	6.2
35–39	20	18	90.0	25	23	92.0	45	41	91.1	4.3
40–49	31	30	96.8	28	23	82.1	59	53	89.8	4.1
50–59	41	39	95.2	22	21	95.5	63	60	95.3	2.7
60–69	35	35	100.0	16	16	100.0	51	51	100.0	
70–79	40	40	100.0	11	11	100.0	51	51	100.0	
80–89	9	9	100.0	3	3	100.0	12	12	100.0	

* Standard deviation of the rate $= \sqrt{\frac{pq}{n}}$ where p = per cent infected, q = per cent not infected, and n = number of cases.

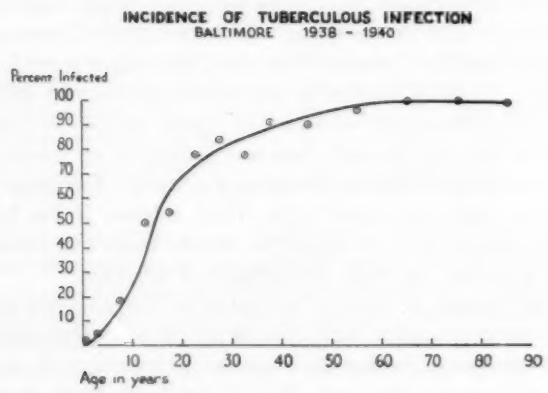


FIG. 1

with greater accuracy the probable trend in rates. It has been made to pass through zero per cent at birth since the incidence of congenital infections is known to be insignificantly small.

The results may be conveniently summarized from the figure. The curve indicates a rapid increase in the rate of acquisition of infections in the first few years of life. The steepest part of the curve lies between the ages of 10 and 15 years and indicates an increase in that brief span of about 25 per cent in the infected portion of this population. The curve also indicates that by the age of 20 years something approximating 70 per cent of the individuals are infected. After this age the increase in incidence rises more and more slowly to approach 100 per cent after the age of 60 years. The incidence of

TABLE 2

Incidence of tuberculous lesions in the mesenteric lymph nodes in 153 autopsies

	AGE							
	0–1	1–4	5–9	10–14	15–19	20–29	30–39	40–89
Number of cases	24	25	19	0	16	27	36	6
Number positive	0	0	0	—	0	2	2	0
Per cent positive	0	0	0	—	0	7.4	5.6	0

infection among the entire adult population of this community[3] is estimated at approximately 90 per cent.

No analysis of the type or location of the lesions has been made for the purpose of this presentation but the mesenteric lesions have been so few as to deserve a mention. In order that the observations may be judged on the same standards as those of the rest of the survey, only those cases in which the mesenteries were X-rayed are analyzed in Table 2. All these lesions had the characteristics of a primary intestinal complex but in two of the four there was also evidence of a primary type of pulmonary infection. The table shows that such lesions are uncommon in the adults and very rare in the children of this series. None were found in 84 individuals under 20 years of age

[3] Calculated on the basis of the population characteristics of urban Maryland, preliminary report, U. S. Bureau of the Census, 16th census of the U. S., 1940.

and among 69 adults above 20 years only 4 (5.8 per cent) possessed such lesions. Two of these were white and two negro.

DISCUSSION

The primary object of this study has been to determine the incidence of tuberculous infection in Baltimore at the present time. It was also hoped that a comparison of this information with the results of previous studies in the past, particularly that of Opie in 1916 in St. Louis, might throw some light on the degree of change in the incidence of infection that has accompanied the dramatic decline of mortality and morbidity from tuberculosis since these early studies were made. For reasons that will become apparent in the subsequent discussion, there has only been a partial fulfillment of either of these objectives. The factors operating to limit this success are those inherent in the method of search, those due to the selection of material, and those imposed by statistical standards.

There is no doubt that a thorough postmortem search offers the most accurate information regarding the incidence of tuberculous infection. Even this method is beset with limitations, however, which it is necessary to recognize. The major premise on which the value of this method depends is that an infection with the tubercle bacillus leaves its trace in the form of a recognizable lesion. That this is generally true is suggested by the frequency of such lesions in the cases examined by Naegeli and some other investigators. That it is necessarily true seems unlikely from the fact that in most investigations, including the present one, a few cases have been seen in which no recognizable lesion occurred in the lung parenchyma, while a definite healed lesion was found in the hilar lymph nodes. There is a distinct possibility, therefore, that even with perfect technique the search may fail to identify every infected individual. It is impossible to estimate the magnitude of this error but it can only be of significance when the observed incidence of lesions is low. The importance of the thoroughness with which the search is conducted scarcely needs to be emphasized, although more than one investigator has gone to the trouble to demonstrate how greatly the results can be affected by the exercise of painstaking care in the search for minute healed lesions (1, 5, 10, 13). The use of the X-ray on the resected specimens is of

tremendous help for this reason. The inclusion of the lungs, all bronchial and tracheal lymph nodes, and the mesentery in this search will reveal virtually every existing primary lesion since the primary complex occurs in these locations in nearly all infections (35).

When all the lesions are located the next problem is the diagnosis of their tuberculous etiology. The typical gross and microscopic characteristics of the tuberculous lesion in many instances offer little difficulty. The completely healed lesions, however, have caused some hesitancy on the part of several investigators. Sharply circumscribed, encapsulated, calcified lesions in the parenchyma of the lungs and the regional lymph nodes may be safely regarded as tuberculous in the vast majority of instances, as many studies have now proven (11, 12, 13) except in areas where infection with the *Coccidioides immitis* is prevalent (33). The etiology of purely fibrous scars, especially at the apices of the lungs (the *schiefrige Indurationen* and *Spitzennarben* of the German literature) has much less uniformity of opinion. It is not infrequently observed that such scars contain microscopic tubercles of characteristic form but in some series of reported cases (11, 15) many of these scars have been recorded in the absence of any other evidence of tuberculosis. One cannot be certain that a more thorough microscopic search would not have revealed tuberculous lesions in a portion of these. Moreover, it is by no means certain that these scars are non-tuberculous even in the absence of specific lesions since typical tuberculous lesions in the laboratory animal may resolve and leave only non-specific scars and pleural thickenings (36). However, conservatism prohibits the classification of these lesions as positively tuberculous. Fortunately, in the present series of cases, few of these non-specific apical scars were found unassociated with other more positive evidences of tuberculosis. The addition of the few cases in which these were the only lesions to the positive cases in the series makes only a small difference in the curve of the incidence of infection (Table 3). These sources of error in the location and identification of tuberculous lesions are all of such a kind as to produce a lowering of the observed incidence of infection. For this reason the results reported must be taken as a minimum figure.

The selection of the material to be examined is a matter of considerable importance about which there is great limitation of choice.

Since it is restricted to the autopsied deaths in the community, it will be derived from whatever sources the hospital admissions are derived. In some communities, especially in the European cities, these are composed almost entirely of the poor and the destitute. In most reported studies they have included almost exclusively patients resident in large cities. In a few instances they have included largely patients from rural communities (3, 10, 37). However, in no instance can it be said that studies of this sort were perfectly representative of any community or any class within a community. Similarly the present study is not exactly representative of the whole or any particular part of Baltimore. The Baltimore City Hospitals admissions are made up almost exclusively of residents of the city of Baltimore and very largely of patients who cannot pay for hospital care. The Johns

TABLE 3

Increase in the observed incidence of infection caused by the addition of cases with only non-specific apical pulmonary scars to the positive group

AGE	PER CENT POSITIVE FROM TABLE 1	NUMBER OF CASES WITH ONLY APICAL SCARS	PER CENT POSITIVE INCLUDING CASES WITH ONLY APICAL SCARS
25–29	83.8	2	89.2
30–34	77.7	2	82.2
35–39	91.1	1	97.7
40–49	89.8	2	93.2
50–59	95.3	2	98.4

Hopkins Hospital admissions include considerable numbers of patients who pay part or all of their hospital expenses and a small proportion of suburban and out of town residents. The percentages of autopsies in the deaths among these several classes of patients are not very different. It would be most desirable to know in what degree the results have been influenced by differences in economic class and in length of residence in Baltimore. The hospital records do not furnish sufficient data to determine this with any precision. However, a search of the records of all of the 35 negative adults has been made with the result that less than 15 per cent of these were found to be private cases and no more than 15 per cent out of town residents. Of the eleven negative adults who were residents of Baltimore, for whom a minimal period of residence in the city could be estimated from the available information, the average term of residence was more than 25 years. Only two had

lived in the city less than 16 years. Although these data give us no information on the relative frequency of infection in the different economic and residential groups, they do satisfactorily rule out the possibility that the appreciable fraction of noninfected adults was significantly influenced by the inclusion of private and non-resident cases in the series. They also show that at least nine adults of the series who had lived in the city of Baltimore for periods of 16 to 54 years, had no anatomical evidence of previous tuberculous infection.

A vastly more important point in the selection of material for this sort of survey is the exclusion of cases dying of tuberculosis. The annual mortality from tuberculosis in any age group is far less than one per cent of the individuals in that age group. The complete omission of fatal cases of tuberculosis from this series causes no significant error in the observed incidence of infected individuals in any age group in which the true incidence of infection is high in relation to the mortality rate. For this reason it could cause an important error only in the infant group. The inclusion of these cases, on the other hand, may cause a very great elevation in the apparent incidence of infection unless the true incidence itself is very high. The magnitude of this error may be appreciated by the recollection that tuberculosis is still a major cause of death in certain age groups. For example in Baltimore in 1936, 21 per cent of the white and 39 per cent of the negro deaths at the age of 20 to 24 years were due to tuberculosis. Even in hospitals where the admission of patients with pulmonary tuberculosis is avoided, the deaths from other forms of tuberculosis are not inconsiderable, especially among the children. There can be no justification for including fatal cases of tuberculosis among the positive portion of such a series as this out of proportion to their actual incidence in the population. This error has been committed, however, in many of the similar surveys in the past. It has been avoided in the present study by the elimination of fatal tuberculosis from the series. The small error caused by this omission has not been corrected because to make this correction would require a knowledge of the incidence of morbidity from tuberculosis in each age group, which we do not have.

Finally a consideration of very great importance is the statistical value of the figures obtained. If one grants that the material is well chosen and correctly examined, what is the reliability of any observed

incidence purely on the basis of the chances involved in sampling? This reliability is a function of the number of cases examined and the observed incidence, and some measure of its height in the present data is expressed by the standard deviations in Table 1 (34). It is evident that in several age groups the values for the standard deviation are so large as to render the isolated figure useless. For this reason it would be highly desirable to have a larger number of individuals in several of the age groups. The low death rate among the younger people has made this ideal impossible to attain with the available material in the period of time that could be devoted to this study, which was interrupted by the writer's change of residence. The deficiency in numbers of cases in all age groups of the present study is keenly appreciated but the data were judged useful to record in the absence of any other study of similar extent in this country. Moreover, while the isolated percentage in any age group is subject to great sampling error due to the relatively small number of cases involved, the several points considered together, in view of the consistency of their trend, are subject to less sampling error. Fitting a curve to the points takes advantage of this fact and Figure 1 therefore has greater value in indicating the probable incidence of infection at different ages than the percentages in Table 1.

In summary it may be said that the incidence of tuberculous lesions in the population of Baltimore today is in all likelihood well approximated by the curve of Figure 1. To consider this as representing the incidence of infection requires the assumption that no significant number of infections heal without leaving a recognizable lesion. The practically universal presence of these lesions in old age suggests, but does not prove the truth of that assumption. If this curve does represent the true incidence of infection in Baltimore today, its most important implication is the existence of a considerable body of young adults in this population who have had no previous immunization against tuberculosis. The prevailing doctrine of the pathogenesis of adult tuberculosis would require that these individuals develop the childhood type of disease when exposed. The curve indicates, further, that about 15 per cent of individuals are first infected between the ages of 20 and 30 years. Since this is the decade in which the mortality from tuberculosis is at its highest, it might be anticipated that an

appreciable number of cases of progressive childhood type of disease would develop among this group. Rich (16) has discussed this eventuality as a consequence of the low incidence of tuberculous infection indicated by recent tuberculin surveys and has pointed out that, contrary to what might be expected, the tuberculosis of young adults has precisely the same characteristics today in both clinical and pathological experience as it has had in the past. From this it was concluded that either the incidence of infection is higher than is indicated by the recent tuberculin surveys or that a previous immunizing infection is not essential for the development of the adult type of tuberculosis. Since the available tuberculin data were on nonrepresentative groups of the adult population (college students and entrants into medical and nursing schools) it was suggested that the true incidence was probably higher than the tuberculin surveys indicated. The present data from a more nearly representative sample of the population support that opinion. However, the proportion of noninfected young adults which was found in the present study, is sufficiently large still to allow some doubt of the doctrine that previous infection is necessary for the development of the adult type of disease. A further examination of the evidence will be necessary after more extensive information on the present incidence of infection is available.

The second object of the present study has been to estimate what change has occurred in the incidence of infection during the past generation. The difficulties encountered in obtaining precise information about the present are greatly multiplied in attempting to bring the current data into relation with those of the past. The greatest interest centers about a comparison of the present figures with those obtained by Opie (4) in St. Louis in 1916, since that is the only early anatomical study in the United States. Table 4 compares these two sets of data. The technique of examination and the criteria for diagnosis used in the present study were purposely made to conform to that earlier study in every essential detail. The selection of material was similar insofar as it was designed to obtain a representative sample of the autopsied cases dying in a large urban hospital of diseases other than tuberculosis. The proportions of white and negro cases and the inclusion of private and non-resident cases in Opie's series were not recorded but the most serious limitation to a reliable comparison of the two sets of

data arises from the small samples to be compared. Table 4 shows that the number of individuals examined by Opie in each age group during the most crucial period from 2 to 30 years is so small as to make the observed percentages of very low reliability. The difficulty of obtaining an adequate number of cases in the adolescent age group, because of the low mortality during that period, has already been pointed out. However, since the same fault exists in each of the four age groups in which the largest differences from the current data exist, none of the values for χ^2 given in the last column of the table is significant. (That small numbers of cases may be productive of

TABLE 4

AGE	ST. LOUIS 1916			BALTIMORE 1938–40			χ^{2*}
	No. Cases	No. Pos.	% Pos.	No. Cases	No. Pos.	% Pos.	
Under 1	39	0	0	50	1	2.0	
1–2	15	0	0	21	1	4.8	
2–5	11	3	27.3	21	1	4.8	3.20
5–10	9	3	33.3	22	4	18.2	0.90
10–18	8	5	62.5	23	9	39.2	1.35
18–30	5	5	100	72	60	83.3	1.32
30–50	22	22	100	150	129	86.0	1.31
50–70	14	14	100	114	111	96.5	
Above 70	6	6	100	63	63	100	

* A probably significant difference between two of the percentages is indicated by a value of χ^2 greater than 4 (34).

misleading results is evident in Table 1 of the present study in which the incidence of lesions in certain age groups is smaller in negroes than in whites. From all that we know of the incidence of the disease in Baltimore and elsewhere in this country this is surely not representative of the general population.) Nevertheless it may be seen that above two years of age the deviations in the percentage infected are consistently in the direction of higher values in the earlier series. Similarly a smooth curve drawn through the points of those data would have a considerably higher level than the curve of Figure 1. Such a curve would indicate approximately 85 per cent infection at 20 years of age and would approach 100 per cent after the age of about 35 years. It may be said therefore that there is some indication of a greater inci-

dence of tuberculous infection in St. Louis in 1916 than in Baltimore in 1940, although this may scarcely be taken as decisive evidence. It is worthy of emphasis that the prevalent conception that tuberculous infection is virtually universal in urban individuals in this country by the time adulthood is reached was based entirely on the tenuous anatomical evidence derived from Opie's 1916 study (4) and upon his postmortem X-ray study of the lungs of an additional group of adults in St. Louis in 1924 (38) in which shadows of "calcification" were found in all of 23 individuals examined between 18 and 30 years of age.[4] Even if one could accept these studies as valid evidence that infection was universal in St. Louis by the time adult life was reached, there remains the question of local differences in different communities. Reference has already been made to the indications of such local differences in European cities and this will be further discussed below. It is unfortunate that interest in this type of investigation was not stimulated in other American cities in the same era.

It was hoped that the numerous and repeated anatomical studies of the incidence of tuberculous lesions in European cities might afford some indication of corresponding conditions in the United States. A similar trend in the mortality from the disease has characterized the statistics of both continents in the past generation or more. After restricting the review to those reports in which the examination of the material was said to have been conducted by the author himself and with complete thoroughness after the manner prescribed by Naegeli, certain impediments to a satisfactory comparison still remain. With one exception (37) none of these studies have made use of the X-ray to locate the lesions and the variance in results may therefore be due in part to differences in the completeness of search. Moreover it was the practice among most investigators to include in the series the cases of fatal tuberculosis coming to autopsy during the period of study. The proportion of these was quite variable in different series and in some amounted to as much as 40 per cent of the whole. A few of the studies have even failed to state the proportion of fatal tuberculosis in the data. It has already been shown how greatly this may influence the

[4] Twenty-six per cent of the "calcifications" in this group were classified as "very small." It seems unsafe to regard such shadows as pulmonary calcifications without confirmation by direct gross examination.

results. For proper evaluation it is therefore necessary to revise all the tables by omitting the fatal cases and recalculating the percentages where this is possible. The first concern is to reconcile the conflicting reports from the many cities in the early period of investigation already mentioned. No criticism has been found of the method or criteria of diagnosis in those studies (1, 2, 3) where high incidences of infection were reported and even after the elimination of the fatal cases from these series the results are essentially unchanged. This much cannot be said for all the reports which indicated lower incidences of infection. It seems probable in the light of subsequent experience (11, 12, 13) that Necker (15), who found such a low incidence of lesions in Vienna in 1904, erred in being too conservative in his criteria and must have failed to diagnose many healed tuberculous lesions. The excessive proportion of apical scars unassociated with other evidences of tuberculosis, reported by Beitzke (11) in Berlin in 1909, is also so discordant with the experience of other investigators as to suggest a negative error in that report. However, the addition of all the questionable cases of these two series to the positive group still indicates an incidence of infection of only about 50 per cent at the beginning of adult life in each of them—a very important difference from the results in Zurich in 1900 (1), Dresden in 1906 (2) and Bern in 1917 (3). Such a result in Vienna is entirely irreconcilable with the tuberculin studies of Hamburger and others (7, 39) in that city in 1909, who found the incidence of positive reactors around 90 per cent by the age of 14 years. A similar inconsistency exists between the results of Nothmann's (8) tuberculin survey in Düsseldorf in 1910 and the much lower incidence of lesions reported by Lubarsch (12) in adults in the same city in 1913. Moreover, the differences indicated between these cities is not in keeping with their respective tuberculosis mortality rates. Vienna has long had the highest rate of any of these cities and the rates for Berlin and Düsseldorf were no lower than those of Zurich and Dresden respectively (40, 41). While there is less firm ground for doubting the reports of low incidences of infection in Posen in 1913 (12), Zwickau in 1913 (12), Magdeburg in 1926 (13), and Chemnitz in 1924 (14), it must be pointed out that the numbers of individuals examined in the latter two series were not large. The mortality rates were somewhat lower in these cities (41) than in those previously mentioned and it

seems that such an extremely low percentage of infections (36 per cent of the adults) as that found in Zwickau must indicate a very significant difference from Zurich, Dresden and Bern. Such a great difference in observations could scarcely be accounted for by an error. Finally, Oslo (10) offers peculiar difficulties in interpretation because of the uncertain composition of its hospital population.[5] The low incidence reported in Oslo in 1910 is also out of keeping with its high tuberculosis mortality (40), which was second only to that of Vienna among the cities discussed here.

In spite of the poor conviction carried by several of these reports the conclusion seems inescapable that there were considerable differences in the incidence of tuberculous infection in a number of European cities in the early part of this century. The uncertainties in regard to some of these reports and the large differences between some of them make it difficult to draw any generalizations regarding the former extent of infection in European city-dwellers. For this reason the reinvestigations in the same cities in several instances in more recent times assume the greatest importance in indicating what effect the changed circumstances of the present era have had. Schürmann (42) in 1926 reported an adult rate of infection in Dresden at least as great as that of Burkhardt (2) in 1906. Unfortunately, the fatal cases were not separated in this report, but with an observed incidence above 90 per cent this would cause an error of no great magnitude. Similarly, Frimann-Dahl and Waaler (37) in Oslo obtained rates in adults in 1936 a little higher than those reported by Harbitz (10) in 1904. The use of the X-ray in the later study may have increased the effectiveness of that search. Uehlinger and Blangey (43), on the other hand, reported considerably lower rates of infection in Zurich in 1937 than those found by Naegeli in 1897–8. Between the ages of 19 and 40 years, for example, Naegeli found 93 per cent, and the later authors only 62 per cent infected. However a further interesting fact revealed by the tables casts some doubt on the comparability of these two series. The section of the population aged 19 to 40 which was found 93 per cent infected by Naegeli corresponds approximately to the group aged 61 to 80 in the later study. The data of Uehlinger and Blangey show only 84 per cent

[5] Later investigators from this city (37) stated that a very large proportion of the patients were from rural communities.

of that group infected. This decrease in incidence of infection in the same group of individuals over a period of years is unexpected and contrary to the trend of infection rates with age which is generally indicated. Such a phenomenon could be explained either by a large immigration of non-infected adults of this age into the population sampled or by a much higher total mortality among the infected portion of that population. Either of these possibilities seems quantitatively improbable. A small systematic error (about 10 per cent) in the finding and identification of the lesions would produce a similar result and would also be consistent with the tendency in this study for the curve of the incidence of infection to approach 90 per cent asymptotically instead of 100 per cent as it would be theoretically expected to do. Whatever the explanation of this failure of consistency between the two reports may be, it does hamper a direct comparison of them. To be added to the other recently acquired data is a small series reported by Winkler (44) from Breslau in 1933 in which more than 70 per cent of adults under 40 years of age were found infected. The indications are, therefore, that in spite of the marked decline in tuberculosis mortality, no drastic decline in the incidence of tuberculous infection has occurred in European cities since the early part of this century. No more exact conclusion can be drawn from the data available.

The uncertainty inherent in the numerous European investigations only serves to emphasize the lack of knowledge about the incidence of infection in the United States. Evidence must be accumulated in numerous localities and by the most careful methods in order to fill this gap. It is to be hoped that such studies, when they are performed, will make use of the X-ray to locate the lesions since this not only saves the investigator much time but also helps to standardize the degree of thoroughness used by different investigators. Terplan (45) has collected data on the incidence of tuberculous lesions in a large series of autopsies in Buffalo, New York, in the past several years. Unfortunately the incidence of lesions in adults dying of other diseases is not calculable from his data but the incidence in the children is so much lower than the Baltimore figures as to suggest a great difference between these cities. It would be most interesting to have complete information in several cities where the mortality rates from tuberculosis

differ as they do between Baltimore and Buffalo. A reinvestigation in St. Louis would be the most valuable of all in indicating what effect may result from the known changes of the past twenty-five years, though even here an accurate interpretation would be hardly possible in view of the limitations of the earlier study, as discussed above. Statistics on the rural part of our population would also hold considerable interest. These will undoubtedly be more difficult to obtain. A study of a small series of cases from a semirural group in Maryland has recently been reported by Landé and Wolff (46). This series must be considerably amplified before conclusions can be drawn as to the incidence at different ages among this population.

SUMMARY

The desirability of further information on the present incidence of tuberculous infection in various communities has been created by a steady fall in mortality from the disease and a great decrease in the proportion of tuberculin sensitive individuals. The serious doubt recently cast on the accuracy of the tuberculin test as an indicator of the incidence of infection has made it necessary to resort to the method of postmortem anatomical search in the attempt to establish this incidence. This method of investigation has been employed on a representative sample of the autopsies in two large hospitals in the city of Baltimore, during the period 1938 to 1940. The indications from this study are that about 70 per cent of individuals in this city have acquired a tuberculous infection by the age of 20 years and that universal infection is approximated only in the age group above 50 years. Taking into consideration the age distribution of the adult population the data indicate that about 90 per cent of the adults in this city have been infected. While these results suggest a moderate fall in the incidence of infection in adults since the study of Opie in St. Louis in 1916, the statistical comparison of these data does not yield a conclusive answer. Furthermore, an analysis of the numerous anatomical investigations carried out in European cities since the beginning of this century indicates considerable local differences in the incidence of infection. The more recent European surveys have not indicated any great change in the past generation in spite of a marked decline in tuberculosis mortality. These considerations make it

essential that similar anatomical surveys be conducted in numerous localities in the United States before any conclusion is reached regarding the prevalence of tuberculous infection in this country today. It will be possible to evaluate the effect of lowered mortality and morbidity from tuberculosis on the extent of its distribution in the population only after such studies have been repeated at intervals in the same localities and with identical technical methods. A comparison between the available tuberculin surveys and the anatomical findings suggests that the great decrease in the rate of exposure of the population in recent times may have resulted in a greater decrease in the number of infected persons who maintain their hypersensitivity than in the proportion of infected individuals. This is supported by the increasing frequency with which calcified lesions are being found in individuals who do not react to tuberculin. The bearing of these matters upon the question of the reason for the differences between adult and childhood types of tuberculosis is discussed in the body of this paper.

630 W. 168 St., New York City.

The author is deeply indebted to Dr. Arnold R. Rich for stimulation and advice in the pursuit of this study, and to Dr. John W. Fertig for help with the statistical interpretations.

REFERENCES

(1) Naegeli, O.: Ueber Häufigkeit, Localisation und Ausheilung der Tuberkulose: nach 500 Sektionen der Zürcherischen Pathologischen Instituts. *Virch. Arch.*, **160:** 426 (1900).

(2) Burkhardt, A.: Ueber Häufigkeit und Ursache menschlicher Tuberkulose auf Grund von ca. 1400 Sektionen. *Z. f. Hyg.*, **53:** 139 (1906).

(3) Reinhart, A.: Anatomische Untersuchungen über die Häufigkeit der Tuberkulose. *Corr.-bl. f. Schweiz. Aerzte*, **47:** 1153 (1917).

(4) Opie, E. L.: Focal pulmonary tuberculosis of children and adults. *J. Exp. Med.*, **25:** 855 (1917).

(5) Schirp, K.: Statistische Mitteilungen über phthisische Erkrankungen bie verschieden genauen Sektionsmethoden. *Beitr. z. Klin. d. Tuberk.*, **49:** 308 (1922).

(6) Ganghofner: Ueber die Pirquetsche Tuberkulinreaktion. *Wien. klin. Wchnschr.*, **21:** 1403 (1908).

(7) HAMBURGER, F. and MONTI, R.: Die Tuberkulosehäufigkeit im Kindesalter. *Münchn. Med. Wchnschr.*, **56:** 449 (1909).

(8) NOTHMANN, H.: Ueber die Häufigkeit der Tuberkulose im Kindesalter. *Berl. klin. Wchnschr.*, **47:** 381 (1910).

(9) CALMETTE, A., GRYSEZ, V., and LETULLE, R.: De l'infection bacillaire et de la Tuberculose aux differents ages de la Vie. *Presse Méd.*, **19:** 651 (1911).

(10) HARBITZ, F.: Untersuchungen über die Häufigkeit, Localisation und Ausbreitungswege der Tuberkulose. *Kristiania* (1905).

(11) BEITZKE, H.: Ueber die Häufigkeit der Tuberkulose am Leichenmaterial des Berliner pathologischen Instituts. *Berl. klin. Wchnschr.*, **46:** 388 (1909).

(12) LUBARSCH, O.: Beiträge zur Pathologie der Tuberkulose. *Virch. Arch.*, **213:** 417 (1913).

(13) BLUMENBERG, W.: Die Tuberkulose des Menschen in den verschiedenen Lebensaltern auf Grund anatomische Untersuchungen: II. Die Tuberkulose des Mittleren Lebensalters. *Beitr. z. Klin. d. Tuberk.*, **62:** 711 (1926).

(14) HESSE, F.: Beitrag zur Anatomie, Statistik und klinische Diagnostik der Tuberkulose. *Beitr. z. Klin. d. Tuberk.*, **58:** 244 (1924).

(15) NECKER: Ueber die Häufigkeit der tuberkulösen Veränderungen am Leichenmateriale. *Verh. d. dtsch. path. Gesellsch.*, **8:** 129 (1904).

(16) RICH, A. R.: The influence of age-determined factors on the development of tuberculosis. *Minn. Med.*, **21:** 745 (1938).

(17) DIETRICH, A.: Ueber die Tuberkulosehäufigkeit im Kindesalter. *Med. Klin.*, **33:** 1637 (1937).

(18) CHADWICK, H. D. and ZACKS, D.: The incidence of tuberculous infection in schoolchildren. *N. Eng. Med. J.*, **200:** 332 (1929).

(19) OPIE, E. L., and MCPHEDRAN, F. M.: The contagion of tuberculosis. *Am. Rev. Tuberc.*, **14:** 347 (1926).

(20) BARNARD, M. W., AMBERSON, J. B., JR., and LOEW, M. F.: Tuberculosis in adolescents. *Am. Rev. Tuberc.*, **23:** 593 (1931).

(21) CRABTREE, J. A., HICKERSON, W. D. and HICKERSON, V. P.: Tuberculosis studies in Tennessee. *Am. Rev. Tuberc.*, **28:** suppl. 6 (1933).

(22) NELSON, W. E., MITCHELL, A. G., and BROWN, E. W.: The intracutaneous tuberculin reaction associated with calcified intrathoracic lesions. *Am. Rev. Tuberc.*, **37:** 311 (1938).

(23) GASS, R. S., GAULD, R. L., HARRISON, E. F., STEWART, H. C., and WILLIAMS, W. C.: Tuberculosis studies in Tennessee: roentgenological evidence of tuberculous infection in relation to tuberculin sensitivity in schoolchildren. *Am. Rev. Tuberc.*, **38:** 441 (1938).

(24) LLOYD, W. E., and MACPHERSON, A. M.: A reinvestigation of children previously examined by tuberculin tests. *Brit. Med. J.*, **1:** 818 (1933).

(25) Aronson, J. D., and Dannenberg, A. M.: Effect of vaccination with BCG on tuberculosis in infancy and childhood. *Am. J. Dis. Child.*, **50:** 1117 (1935).

(26) Horan, T. H.: The incidence of tuberculous infection and disease in a private school for boys. *Am. Rev. Tuberc.*, **32:** 166 (1935).

(27) Paretzky, M.: The disappearance of specific skin hypersensitiveness in tuberculosis. *Am. Rev. Tuberc.*, **33:** 370 (1936).

(28) Keller, A. E., and Kampmeier, R. H.: Tuberculin survey: observations on medical students and undergraduate nurses at Vanderbilt University. *Am. Rev. Tuberc.*, **39:** 657 (1937).

(29) Dahlstrom, A. W.: Instability of the tuberculin reaction: observations on dispensary patients, with special reference to the existence of demonstrable tuberculous lesions and degree of exposure to tubercle bacilli. *Am. Rev. Tuberc.*, **42:** 471 (1940).

(30) Crimm, P. D., and Short, D. M.: Tuberculin anergy in cases with pulmonary calcifications. *Am. Rev. Tuberc.*, **39:** 64 (1939).

(31) Lumsden, L. L., Dearing, W. P., and Brown, R. A.: Questionable value of skin-testing as a means of establishing an epidemiological index of infection. *Am. J. Pub. H.*, **29:** 25 (1939).

(32) Olson, B. J., Wright, W. H., and Nolan, M. O.: An epidemiological study of calcified pulmonary lesions in an Ohio county. *Publ. Health Rep.*, **56:** 2105 (1941).

(33) Cox, A. J., and Smith, C. E.: Arrested pulmonary coccidioidal granuloma. *Arch. Path.*, **27:** 717 (1939).

(34) Hill, A. B.: Principles of Medical Statistics. *London* (1937).

(35) Sweany, H. C., and Martinsen, W. L. M.: The incidence of extrapulmonary primary tuberculosis. *Am. Rev. Tuberc.*, **37:** 465 (1938).

(36) Gardner, L. U.: Healing by resolution in experimental pulmonary tuberculosis. *Am. Rev. Tuberc.*, **6:** 163 (1922).

(37) Frimann-Dahl, J. and Waaler, G.: Röntgenologische und pathologisch-anatomische studien über den tuberkulösen Primärkomplex. *Acta Radiol.*, suppl. 33 (1936).

(38) Opie, E. L.: Pathological evidence of the first infection in association with active pulmonary tuberculosis. *Am. Rev. Tuberc.*, **10:** 249 (1924).

(39) v. Pirquet, C.: Frequency of tuberculosis in childhood. *J. A. M. A.*, **52:** 675 (1909).

(40) League of Nations, Health Organization, Epidemiological report **10:** 55 (1931).

(41) Medizinal-statistische Mitteilungen aus dem Kaiserlichen Gesundheitsamte, **16** (1913).

(42) Schürmann, P.: Der Primärkomplex Rankes unter anatomischen Erscheinung der Tuberkulose. *Virch. Arch.*, **260:** 664 (1926).

(43) UEHLINGER, E. and BLANGEY, R.: Anatomische Untersuchungen über die Häufigkeit der Tuberkulose. *Beitr. z. klin. d. Tuberk.*, **90:** 339 (1937).

(44) WINKLER, E.: Untersuchungen über die Häufigkeit Tuberkulöser Veränderungen am Leichenmaterial unter Benützung aller Methoden des Nachweises. *Beitr. z. klin. d. Tuberk.*, **82:** 655 (1933).

(45) TERPLAN, K.: Anatomical studies on human tuberculosis. *Am. Rev. Tuberc.*, **42,** Suppl. 2 (1940).

(46) LANDÉ, K. E., and WOLFF, G.: Frequency of tuberculous lesions at autopsy. *Am. Rev. Tuberc.*, **44:** 223 (1941).

A CLINICAL AND ANATOMICAL STUDY OF NEUROLOGICAL CONDITIONS RESULTING FROM METASTASES IN THE CENTRAL NERVOUS SYSTEM DUE TO CARCINOMA OF THE LUNG

Review of One Hundred Cases

ARTHUR B. KING and FRANK R. FORD

From the Neurological Clinic, The Johns Hopkins Hospital and the Department of Medicine of the Baltimore City Hospitals

Submitted for publication December 11, 1941

TABLE OF CONTENTS

Résumé of the Literature 124
Incidence 127
Pathological Anatomy 128
Neurological Features 129
I. Classification of Cases 129
(A) Cases with Signs of a Single Focal Lesion in the Brain 129
(B) Cases Characterized by Multiple Lesions 135
(C) Cases Characterized by Stupor 140
(D) Cases Characterized by Deposits in the Brain and Spinal Cord 144
(E) Cases in which the Cerebral Metastases Were Silent 146
(F) Cases in which the Spinal Cord Alone Was Involved 149
II. Analysis of Symptoms 151
III. Laboratory Studies 152
Non-Neurological Features 153
Summary and Conclusions 154
Bibliography 156

RÉSUMÉ OF THE LITERATURE

From time to time during the past few years patients have been observed who presented puzzling neurological symptom complexes, variously diagnosed as intracranial neoplasms, cerebro-vascular accidents, encephalitis and drug poisoning. At autopsy metastases to the nervous system from unsuspected carcinomas of the lung were found. This led us to review the files of the departments of Pathology of the Johns Hopkins Hospital and the Baltimore City Hospitals in order to determine whether these cases might have been diagnosed correctly ante mortem.

There are several reports in the literature by clinicians who have encountered similar cases. Heinemann (1911) was one of the early authors who pointed out that carcinomas of the lung could pursue a latent course, the only symptoms being those caused by metastasis to the central nervous system. An individual who was quite well until he sustained a stroke, was described by Morse (1923). The patient went on to develop delirium, visual hallucinations, headache and vomiting, and finally became completely disoriented. Late manifestations were papilledema, cervical rigidity, Kernig's sign, and signs referable to the cerebellum. Post mortem examination revealed numerous small nodules of carcinoma in the brain, meninges, spinal cord, cauda equina and cranial nerves.

Grant operated upon a patient for a tumor of the left frontal lobe and discovered that it was a metastatic growth. Later symptoms referable to the primary carcinoma in the lung developed. In reporting this case he states that 4 per cent of brain tumors have a malignant origin elsewhere in the body. Dosquet is quoted as having found that 31.4 per cent of 105 cases of carcinoma of the lung produced cerebral metastases. The sudden onset of psychosis was stressed by Grant as a prominent feature of metastatic lesions in the brain. This was also pointed out by Davidson and Horwitz (1930) who presented a case in which there were all the signs and symptoms of dementia paralytica, but at postmortem there was found a carcinoma of the lung with cerebral metastasis. Seven autopsy records were included in his paper, three patients had single cerebral metastases, three had multiple nodules, and one had metastases to the spinal cord alone.

Globus and Selinsky (1927) in reviewing 12 cases of malignant tumors of the brain included two cases of bronchogenic carcinoma. They stressed the frequent finding of meningeal irritation and pleocytosis of the cerebro-spinal fluid. In their experience the onset of symptoms was acute and the signs diffuse. Symptoms of increased intracranial pressure were often predominant. They found that papilledema was distinctly unusual.

Fried and Buckley (1930) reviewed 38 proven cases of primary lung carcinoma and found that 15 of the patients had metastases to the central nervous system. In 12 patients neurological signs pre-

dominated. They pointed out that the onset of symptoms was frequently sudden, occurring in 9 of the 15 cases. Six of this latter group had convulsions or a sudden hemiplegia as the first manifestation of the disease. The lack of pulmonary symptoms and signs and the excellent state of nutrition of the patients were also stressed.

Alpers and Smith (1936) review the history and course of a patient who was first seen with the complaint of pain in the lumbar region. This was followed by paraplegia and difficulty with speech. Although a metastatic carcinoma was suspected it could never be demonstrated. Autopsy revealed a malignant neoplasm of the lung which had produced carcinomatosis of the meninges of the spinal cord and base of the brain. No carcinoma deposits were found in the substance of the brain.

Roger, Cornil and Paillas (1939) studied 28 cases of metastatic tumors of the brain and found over a third were due to a primary neoplasm of the lung. These tumors headed their list as the most common cause of cerebral metastases.

The need for a thorough general physical examination before patients were subjected to cranial operations was stressed by Craig, Woltman and Kernohan (1939). They record the case of a 49 year old woman who came to the Mayo Clinic with the signs of a cerebellar tumor. X-ray of the chest revealed no abnormalities. At operation a metastatic carcinoma was found in the right cerebellar hemisphere. Necropsy demonstrated an adenocarcinoma of the lung, which had metastasized to the hilar nodes, the opposite lung and the cerebellum. No other nodules could be found. Another patient was described who presented the symptoms of a gasserian ganglion tumor. General examination was negative, and at operation a malignant tumor of the left gasserian ganglion was found. At autopsy four months later, a carcinoma of the lung was discovered. The only metastasis was the one in the gasserian ganglion. Other patients who were thought to have tuberculosis, neuritis, and paraplegia were described, who at postmortem showed primary neoplasm of the lung with metastases to the brain, cord, meninges, cranial and spinal nerves.

Ewing (1940) states that cancer of the lung may occur at almost any age but that the majority of tumors are found between the ages

of 40 and 60 years. The condition is much more frequent in males and Stout is quoted by Ewing as noting that the ratio is 83 per cent males to 17 per cent females. In the same article, Adler's work on 374 cases is summarized. The brain contained metastases 53 times. The bones contained tumor nodules in 57 cases, the ribs, spine and skull being most frequently involved. Adler did not find metastases in the skin, spinal cord or hypophysis.

In this study, we have reported only those cases in which there was a complete postmortem study of both the chest and the central nervous system. As the tumors were classified differently by the pathologists throughout the years, we have not attempted to differentiate cancer of the lung into various types. Pleural endotheliomas and sarcomas have been excluded.

TABLE I

Age, Sex and Race Incidence of Lung Carcinoma. 100 Cases

AGE INCIDENCE		SEX AND RACE INCIDENCE	
20–29 yrs.	2	White males	62
30–39 yrs.	14	Colored males	26
40–49 yrs.	25	White females	6
50–59 yrs.	42	Colored females	6
60–69 yrs.	13		
70–79 yrs.	3		
Age undetermined	1		

INCIDENCE

The frequency of carcinoma of the lung is indicated by the statement that in a series of 27,000 post-mortem examinations at the Johns Hopkins Hospital and the Baltimore City Hospitals, 158 cases were discovered, an incidence of slightly more than one half of one per cent. In 100 of these cases, a complete post-mortem examination of the nervous system had been made, and our study is based upon these cases. The age, sex and race incidence of the cases of lung carcinoma studied are indicated in Table I.

Metastatic deposits in the nervous system were found in twenty-seven. These figures are comparable with those compiled by other writers so we may conclude that in approximately one-third of all

cases of carcinoma of the lung the nervous system is involved. It is our belief that carcinoma of the lung metastasizes earlier and more frequently to the brain than does any other common malignant growth, no doubt because the malignant cells may be transported directly by the blood stream without passing through the capillary bed of the lungs. Since the secondary deposits of this particular growth seem to occur in the brain more frequently than in the viscera it is possible that the brain is an especially fertile soil for them.

PATHOLOGICAL ANATOMY

The metastatic deposits in the brain were multiple in twenty of twenty-seven cases and were usually small, rarely exceeding 1 cm. in diameter. They varied widely in size as if of different ages. These deposits were scattered indiscriminately throughout the brain, in the cortex, central white matter of the hemispheres, brain stem, cerebellum and hypothalamus. In one case hundreds of minute metastases were found which were not visible to the unaided eye. The smaller tumor nodules were always solid except in one case in which they were cystic and contained mucus. We found eight tumors which exceeded 2.0 cm. in diameter. The largest of these were 4.0 cm. in diameter. These larger deposits frequently showed central necrosis and at operation the necrotic material was sometimes mistaken for the pus of an abscess. The cranial nerves were involved in several cases usually as a result of pressure by tumors in the adjacent cortex or in the meninges and rarely as a result of deposits in the base of the skull or actual implants in the nerves themselves. In our series, deposits were found in the skull only four times. When the spinal cord was involved the metastasis responsible was found in the spinal meninges or in the vertebrae, never in the substance of the cord. In only one case did we find any condition resembling the tumor meningitis which has been described by other authors. In this case, innumerable minute tumor nodules were found in the pia-arachnoid of the base and these extended into the sulci and perivascular spaces of the brain.

In four cases, deposits were found in the hypothalamus and in two the anterior lobe of the hypophysis was invaded. No doubt, the somnolence or stupor which these patients exhibited was due, in part, to these lesions. The adrenal bodies were involved in more than half

of our cases and it is not unlikely that injury to these glands may have played a role in the patients' weakness and cachexia. The thyroid was affected only twice and the pancreas four times.

The viscera rarely escape. The lungs contain not only the primary growth but numerous secondary deposits as well. The kidneys, liver, spleen and heart are affected in the order given. The mediastinal lymph nodes are almost always invaded and the neck, axillary and inguinal glands are involved in about one third of the cases. In two cases, tumor nodules in the skin were detected and biopsy led to the diagnosis. No doubt, many more were overlooked. As a general group carcinomas of the lung metastasize to the bones approximately as frequently as to the brain. In our series of twenty-seven cases in which the nervous system was involved, however, the incidence of bony lesions was very low. Possibly this discrepancy may indicate a difference in the type of carcinoma.

It is not the purpose of this paper to discuss the character of the lesion in the lungs. It may be said, however, that in certain cases the primary growth is so small that it cannot be detected by clinical means and may even be overlooked at post-mortem examination, even though extensive metastases may have occurred.

NEUROLOGICAL FEATURES

I. Classification of Cases

(A) Cases with Signs of a Single Focal Lesion in the Brain

In eight cases the neurological signs were consistent with a single lesion in the brain. The onset was marked by convulsions in five cases and in three of these focal signs followed immediately. In two cases there was hemiparesis and in one hemianopia and apraxia. Aphasia developed once. In one case a deposit in the left frontal lobe was associated with ataxia which resembled cerebellar ataxia so closely that Cushing explored the posterior fossa. Papilledema was present in only two cases and in one of these it developed late in the course of the illness.

In general it may be said that the focal signs developed rather rapidly and were often preceded by convulsions. The picture resembled that produced by a primary neoplasm of the brain or by vascular

disease. In three cases, the correct diagnosis was made, twice because the lesion in the lungs was discovered and once because a metastatic nodule in the skin was recognized by biopsy. In three cases, the diagnosis of primary tumor of the brain was made and once cerebral softening and general paresis were diagnosed because of the presence of hypertension and of serologic reactions typical of general paresis.

A. F., white, male, 43 years of age. Johns Hopkins Hospital U-12938. Admitted June 30, 1927. Died July 1, 1927. For two months, the patient had been bothered by diplopia. Two weeks before admission he had received a hammer blow on the head, which caused unconsciousness for several hours. He was able to resume work the next day but the same evening he had a convulsion involving the left arm and leg. Afterwards he had become drowsy and had frequent convulsions.

Examination at the hospital revealed a semi-stuporous man who was having frequent convulsive movements of the left arm. Between seizures the arm was spastic. Otherwise nothing was found. Later in the day convulsive movements were observed of the left leg and the left side of the face. At this time, the tendon reflexes on the left were increased.

The next morning the patient had left hemiplegia. Ventriculography was performed and the ventricular system was normal. The ventricular fluid contained 20 lymphocytes per cubic mm. Later in the day the patient lapsed into coma and died.

At autopsy a carcinoma of the lung was found arising from the bronchus of the right middle lobe. Metastases to the mediastinal lymph nodes, liver, kidneys, pancreas, pleura, and pericardium were demonstrated. The brain was covered by a multitude of small nodules scattered over the cerebrum and cerebellum. Myriads more were found when the brain was sectioned; many of these were not larger than a pin head. Several projected under the ependema. Many were found in the cerebellum and in the brain stem.

J. P., white, male, 49 years of age. Johns Hopkins Hospital U-52862. Admitted November 26, 1924. Died February 20, 1925. The patient was admitted to the medical service with the complaint of hemoptysis, loss of weight, and pains in the arms and legs. The duration of symptoms was uncertain. The history was unreliable due to language difficulties.

Examination revealed clubbed fingers, signs of consolidation of the left upper lung, loss of weight, an enlarged prostate gland, and moderate anemia. X-ray of the chest showed a mass in the left upper lobe extending into the apex. A diagnosis of carcinoma of the lung was made and the patient was discharged.

He was readmitted on February 4, 1925 because of headaches. Neurological examination was negative. X-ray studies of the chest showed enlargement of the shadow in the left lung. Slowly he sank into a stuporous state. He would not respond to questions, possibly because of aphasia.

Necropsy (Path. 8609) revealed extensive pulmonary tuberculosis, and a small carcinoma of the lung. No metastases were found except for a single cystic, necrotic mass in the left superior temporal convolution of the brain. This measured approximately 4 cm. in diameter and might have produced aphasia.

I. S., White, female, 35 years of age. Johns Hopkins Hospital U-55684. Admitted January 23, 1922. Died February 11, 1922. During the month of August, 1921, the patient began to complain of headaches. Shortly after this, bouts of vomiting occurred, and following this she developed a staggering gait. By September, 1921, her vision had become reduced and later that month Cushing explored the posterior fossa with negative results. X-ray therapy was given without beneficial effect. Two weeks before admission to the Johns Hopkins Hospital the headaches had become much more severe and her vision had begun to fail. Since operation the patient had been unable to walk because of ataxia.

Examination on admission revealed only bilateral papilledema, bilateral cerebellar ataxia and a positive Romberg sign. A ventriculogram showed evidence of a mass in the right frontal lobe of the brain.

The entire right frontal lobe containing the tumor was resected. Death occurred ten days later from pneumonia.

Post-mortem examination revealed a bronchogenic carcinoma with deposits in the mediastinum, hilar lymph nodes, spleen and adrenal glands. There were no other metastases in the brain.

J. A., white, male, 58 years of age. Baltimore City Hospitals 44296. Admitted May 8, 1939. Died May 15, 1939. The patient had been an inmate of the Infirmary for many months. For about a year he had had a mild cough productive of a small amount of white slimy sputum. Several physical examinations had disclosed nothing abnormal. On the day of admission to the hospital he had a sudden convulsion, which started in the right arm, and then spread to all the extremities. Following the clonic movements, he fell to the floor unconscious.

Physical examination disclosed a questionable left facial paresis of the central type. On the abdominal wall two small hard nodules were felt in the subcutaneous tissues. Tendon reflexes in the legs were absent. Laboratory studies disclosed nothing of significance. The cerebrospinal fluid pressure was 72 mm. H_2O. The fluid contained 2 cells per cu. mm. and the Pandy was negative as well as the Wassermann reaction. X-rays of the chest disclosed an area of clouding in the left midlung region suggestive of a bronchogenic neoplasm. Films of the skull disclosed osteolytic and osteoblastic metastases. Biopsy of the nodules in the abdominal wall revealed metastatic carcinoma. Clinical Impression: Metastatic carcinoma to the brain, probably bronchogenic in origin. The patient grew rapidly weaker and died.

Autopsy (8837) disclosed in the upper lobe of the left lung a mass 6 cm. in diameter arising from a small bronchus. Metastases were found in the hilar lymph nodes, in both adrenal glands, and in the wall of the cecum. Several trans-

lucent, reddish tumor masses were found in the skull. No lesions were found in the dura, brain or spinal cord.

C. B., colored, male, 42 years of age. Baltimore City Hospitals 55551. Admitted May 11, 1940. Died June 24, 1940. The present illness began two weeks before admission with a sudden convulsion, after which a right frontal headache had been present. The patient had had a cough for several months with occasional night sweats but no hemoptysis. There had been no loss of weight. A second period of unconsciousness followed by slight speech difficulties had occurred about a week before admission.

The physical examination showed a well developed and well nourished colored male whose temperature, pulse and respirations were normal. The blood pressure was 107/70. Auscultation of the chest revealed tubular breath sounds over the right middle lobe, a few râles were heard. The cranial nerves were intact except for a mild lower left facial weakness. The left arm and leg were not quite as strong as the right extremities. The gait was a little unsteady but the Romberg was negative. Sensory tests and reflexes were entirely normal.

Laboratory studies disclosed a normal urine. The blood contained 4.72 million red cells, 6,600 white cells per cu. mm., 12.5 grams of hemoglobin per 100 c.c. of blood. The Wassermann reaction of blood and spinal fluid was negative. The cerebrospinal fluid pressure was 350 mm. of H_2O. The fluid was clear. The Pandy was slightly positive. There were 12 mononuclear cells per cu. mm. X-ray of the chest showed a dense area in the right middle lobe which was interpreted as pneumonic consolidation. The clinical impression was bronchiectasis and a brain tumor of the right frontal lobe.

An X-ray of the chest taken one week later showed no change. It was then decided to do a ventriculogram. The right ventricle was easily reached, but the one on the left could not be located until 80 cc. of fluid had been removed by lumbar puncture and an equal amount of air had been introduced. The X-rays did not show any gross abnormalities in the ventricles, but there were small irregularities in the outlines.

It was decided to reinvestigate the pulmonary shadow. Bronchoscopy revealed that the bronchus to the right middle lobe was occluded, suggesting a tumor. Following this, the patient rapidly lost ground. A note dated June 22, 1940 mentioned marked papilledema with numerous hemorrhages about the discs.

The patient suddenly died six weeks after admission.

Autopsy (9494) demonstrated a bronchogenic carcinoma of the midportion of the right middle lobe. Metastatic masses were found in both lower lobes of the left lung, in the hilar glands, in the mesentery, both adrenals and kidneys. Four masses were found in the intestinal walls, and a tumor 7 cm. in diameter along the greater curvature of the stomach. The convolutions of the brain were flattened, and in the left posterior parietal lobe a nodule 3.5 cm. in diameter, projecting through the cortex, was seen. A small flat mass was present in the tip of the right parietal lobe. Additional masses were found in the left frontal lobe above the corpus callosum, one in each hemisphere, projecting into the ventricles, and many

small nodules all through the white matter. A single tumor mass 8 mm. across was found in the pons.

R. T., white, male, 42 years of age. Johns Hopkins Hospital 47907. Admitted February 18, 1933. Died, March 6, 1933. One year before the patient was seen he developed a mild cough which at times was productive of blood streaked sputum. Six weeks before admission he had a sudden severe headache followed by unconsciousness lasting for one hour. There was no preceding aura of convulsive movements at that time. His wife related that he lay still, head bent back, eyes open and a slight froth at the mouth. He remained dazed for several hours. After that there were occasional headaches over the eyes and in the temples. They came on suddenly, lasted a few minutes and then passed off suddenly. Five weeks before admission a second attack of unconsciousness occurred. Following this he was dizzy, and was unable to read.

For the past two weeks before admission he had been unable to tell playing cards apart, distinguish between a knife and a fork, tried to shave with a glass, etc.

Three weeks before admission to the hospital right homonymous hemianopia was discovered. Vision was reduced to 20/200 in either eye. Four days previous to admission he had complained of an odor of "burning." Throughout this period there had been occasional bouts of vomiting.

Physical examination: The patient was unable to smell, to read, or to differentiate letters. Speech seemed normal, and he was oriented. The sensory examination revealed no defects.

On admission an hemianopia could not be demonstrated but two days later a right homonymous hemianopia for color was found. X-ray of the chest showed an irregular shadow at the right lung root which was thought to be old tuberculous glands.

Operation without a ventriculogram was done and a flap over the left parietal lobe was turned down. A tumor weighing 10.6 gms., thought to be a metastasis, was shelled out from the region of the supramarginal and angular gyri.

The patient died suddenly 14 days later. Necropsy demonstrated a primary carcinoma of the right lung with metastases to the mediastinal lymph nodes and the stomach. Tumor nodules were found in the right temporal lobe, and another between the parietal and occipital lobes. A third mass was found deep in the right temporal lobe on the same side.

F. M., white, male, 67 years of age. Baltimore City Hospitals 57978. Admitted August 1, 1940. Died August 8, 1940. The only history that could be obtained was from relatives who stated that six months before admission the patient began to show mental deterioration. He talked irrationally and had crying spells that would last from 1 to 2 days. His memory had become very poor and he behaved like a small child. Often he pretended to read the newspaper but it was observed that the paper was frequently upside down. For the past two months he had been incontinent of urine and feces, and had lost the use of the left leg.

On examination the temperature, pulse and respirations were normal. The

blood pressure was 170/110. The patient was confused, disoriented, mentally deteriorated, senile and incontinent. The face had a stupid expression and showed no emotional changes. The pupils were round, regular and equal. They reacted sluggishly to light. Accommodation and visual fields could not be tested. The fundi showed only "silver wire" arteries. The discs were sharp and of good color. The chest showed only emphysema. The heart was enlarged; the pulse was irregular and the peripheral blood vessels were very sclerotic. The neurological examiner reported weakness of the left arm and complete paralysis of the left leg. The muscles in the left leg were hypotonic but showed no atrophy. Sensory tests were useless for the patient was so apathetic that he could be stuck with a pin anywhere without noticing it. The tendon reflexes were increased in both arms and legs and there was a positive Hoffman on the left. The abdominal reflexes were absent. The patellar reflexes were sluggish and the Achilles reflexes could not be obtained. Clonus was not present but there was a Babinski sign on the left.

Laboratory examination disclosed no abnormalities of the blood or urine, except for a positive blood Wassermann reaction. The cerebrospinal fluid pressure was described as "normal." It contained 2 cells per cu. mm., the Pandy was positive and the total protein was 160 mgm. per cent. The Wassermann reaction was positive and the mastic curve was 4555532211. X-ray of the chest was reported as "heart within normal limits, lungs clear."

The clinical impression was generalized arteriosclerosis, general paresis, and occlusion of the right middle cerebral artery.

The patient rapidly failed and died after being in the hospital for 8 days.

Necropsy (9574) disclosed a bronchogenic carcinoma in the left lower lobe of the lung, near the hilar region. Metastatic lesions were found in the glands at the hilum and at the bifurcation of the trachea. The brain was one mass of metastatic nodules. Large tumor deposits were found in the left parietal lobe, right temporal lobe, left thalamus, left centrum ovale, and midline of the cerebellum. Many smaller metastases were scattered everywhere in the brain.

C. J., colored, male, 63 years of age. Baltimore City Hospitals 60864. Admitted November 11, 1940. Died March 24, 1941. The patient was brought to the hospital by a friend who said the patient was "acting wild and seeing things." Examination by the accident room physicians revealed nothing except loss of weight and weakness. For this reason he was admitted to the Infirmary. Here it was found that the patient had a chronic cough. Physical examination demonstrated dullness at the left apex of the chest, with suppression of breath sounds. Many moist râles were heard in the left chest. The impression was that the patient had old fibroid tuberculosis and generalized arteriosclerosis.

An X-ray film of the chest showed an irregular cloudy area at the left apex, and a prominent shadow at the pulmonary conus. After fluoroscopic examination it was decided that the shadow was due to a large left auricle.

On November 25, 1940 the patient had a convulsion and a right sided weakness was noticed but this cleared up in a few hours.

The patient was then admitted to the hospital. No additional physical findings were noted except that a hard, fixed, non-tender mass could be felt in the right lower quadrant of the abdomen. Many films of the gastrointestinal tract were taken with negative results. Finally an osteolytic metastasis was found in the left ilium. An inguinal gland was biopsied and metastatic carcinoma was found. Shortly after this, the patient died after a sudden hemoptysis. At no time were there any neurological findings, except for the hallucinations on admission and the single convulsion. Several X-rays of the chest were taken but the roentgenologist could never make a satisfactory diagnosis.

At autopsy (9956) a bronchogenic carcinoma was found in the left lower lobe. Metastatic nodules were found all through the lung and pleura. Tumor masses were also found in the inguinal glands, pelvic bones, abdominal wall, spleen and adrenals. The brain contained three nodules of tumor, two in the right parietal lobe and one in the left. The mass on the left measured 2 x 3 cm. There was old fibroid tuberculosis of the left upper lung. Nothing remarkable was found in the heart.

(B) Cases Characterized by Signs of Multiple Lesions

In six cases there were signs of multiple cerebral lesions including hemiparesis, difficulty in speech, nystagmus, cerebellar ataxia, hemianesthesia, palsies of the cranial nerves, hallucinations and stupor. In only one case was there frank papilledema, and in another there was slight edema of the discs. In three cases the diagnosis was correct and was verified by biopsy of metastatic deposits in the skin or lymph nodes or by roentgenograms of the chest. In two cases a primary neoplasm of the brain was suspected although in retrospect it is evident that multiple lesions were present. In the last case, the sudden occurrence of hemiplegia on one side and then on the other, led to the diagnosis of multiple vascular lesions due to cerebral arteriosclerosis. It seems correct to say that in cases of this type there is sufficient evidence to justify the clinical diagnosis in most instances.

L. K., white, male, 51 years of age. Baltimore City Hospitals 63843. Admitted February 21, 1941. Died March 22, 1941. Six months before admission, the patient began to complain of headache and slight nausea on arising in the mornings. For two months there had been periods of dizziness. He had not fallen nor did objects rotate during these attacks. There had been no diplopia. For one month the left arm and leg had been weak. Both lost strength at the same time and this had progressed rapidly. Unsteadiness of gait, difficulty in walking and a tendency

to fall to the left had been noticed for three weeks. For a few days before he was seen, a feeling of numbness had spread over the entire left side of the body. No history of cough, hemoptysis or cardiac symptoms could be elicited.

Physical examination was negative except for the neurological findings. These consisted of poor attention, very early bilateral papilledema, more pronounced on the left; inequality of the pupils, the left being larger than the right; bilateral nystagmus on lateral deviation, more marked when looking to the left; lid lag on the right but no definite facial paralysis; moderate weakness of the left arm and leg with considerable hypotonus; poor performance of fine movements on the left, with past pointing, oscillations, drifting and adiadokokenesis. The left arm and leg were very ataxic. The gait had a broad base, with staggering to the left, and difficulty turning to the left. Speech was thick and explosive, suggesting "cerebellar speech." The tendon reflexes were increased on the left. Clonus and a positive Hoffmann and Babinski reflexes were present on that side.

One small non-tender, hard, movable nodule was felt in the skin of the abdominal wall and another was found in the skin over the left shoulder.

Laboratory studies including a Wassermann test were negative. X-ray films of the chest were reported as normal. The spinal fluid pressure was 180 mm. of water. The fluid contained no cells; but the Pandy test was positive and the total protein was 140 mgm. per cent. A diagnosis of a left cerebellar neoplasm was made.

A ventriculogram was done, which showed normal sized ventricles in their usual position. The walls of the ventricles showed several small irregularities.

Speech became more slurrred, and the patient grew stuporous. Visual fields could not be obtained because of poor cooperation. The papilledema increased rapidly, and many fresh hemorrhages and exudates were noted in both fundi. Further X-ray studies of the chest revealed nothing. The nodule in the abdominal wall was removed for microscopic study and the pathologist reported metastatic carcinoma, probably of the lung. A lipiodol bronchogram visualized the bronchi on the right and in the left lower lobe and these were normal. The patient died suddenly shortly after this.

Necropsy (9939) disclosed an "oat cell" carcinoma of the left upper lobe of the lung. There was a single metastasis to an adrenal gland and another to the skin. The brain had tumor nodules in every portion, too many to be recorded individually.

G. A., white, male, 60(?) years of age. Baltimore City Hospitals 35290. Admitted July 18, 1938. Died September 9, 1938. The patient was found in a field, unable to talk and with a paralysis of the right side of the body. He later stated that four days before admission, his right side had become paralyzed but that he could talk without difficulty. Speech was very difficult to understand and the patient was confused and disoriented.

Physical examination disclosed a well developed and well nourished man of

approximately 60 years of age, whose temperature, pulse and respirations were normal. The blood pressure was 140/85. There was no glandular enlargement. Examination of the chest was negative. Neurological examination showed poor memory, slurred speech and incontinence of urine. The left pupil was larger than the right. Pupils reacted sluggishly to light. Visual fields could not be tested. The fundi showed no abnormalities save a patch of exudate above the left disc. Diminution of touch and pain was found over the right side of the face. A right facial weakness of the central type was noted, as well as deviation of the tongue to the right. All extremities could be moved but there was marked weakness of the right arm and leg. Light touch and pain were diminished over the entire right side of the body. Tendon reflexes were reduced on the right and a positive Babinski was obtained on the same side. No aphasia was reported.

Laboratory studies of the blood and urine were normal. The Wassermann reaction was negative. The cerebrospinal fluid pressure was 150 mm. of H_2O; the Pandy reaction was 2+, there were no cells in the fluid and the Wassermann was negative. The clinical impression was generalized and cerebral arteriosclerosis; right hemiparesis due to thrombosis of the left middle cerebral artery. The patient improved slowly but on August 21, 1938 he suddenly lost the use of his right arm. At this time the only additional finding was a bilateral extensor plantar response. On September 9, 1938 he began to have difficulty in swallowing, and the right-sided weakness became a complete paralysis. Soon he became drowsy and confused and breathed noisily. Facial diplegia, paresis of the tongue, generalized muscular paralysis and stupor developed in rapid succession. Neurological examination at this time showed sluggish tendon reflexes in the arms, absent knee and ankle jerks and bilaterally positive Babinski responses. The fundi were negative except for a few small scattered retinal hemorrhages. The cerebrospinal fluid findings were: pressure 350 mm. of H_2O, no cells and a positive Pandy reaction. The clinical impression at this time was pseudobulbar palsy due to bilateral vascular accidents. A brain tumor was suspected because of the high spinal fluid pressure, but the signs were not definite. Following this the patient developed bronchopneumonia and died. Unfortunately no chest X-rays were taken during the hospital admission. A bronchogenic carcinoma was found in the left upper lobe of the lung at autopsy (8375). A metastasis was present in the right kidney. The brain was one mass of tumor nodules. A nodule 18 mm. in diameter was found in the pons and midbrain cutting across the substantia nigra, the left red nucleus and extending into the thalamus, pushing in the third ventricle and cutting across the left internal capsule. Other masses were found in the left occipital lobe, left frontal lobe, hypothalamus, behind the anterior commissure and in the subthalamus.

W. F., white, male, 52 years of age. Johns Hopkins Hospital U-49886. Admitted February 24, 1923. Died August 31, 1923. The patient was admitted to the hospital with the story of dyspnea, and cough of one year's duration. There

had been some weight loss. Five weeks before he was seen, the patient noticed a lump in the left side of his neck. This had grown rapidly.

Examination revealed several enlarged lymph nodes in the neck. Physical signs pointing to a mass in the right lung and mediastinum were discovered. The veins of the neck, chest, and retina were dilated, and it seemed obvious that there was an obstruction of the superior vena cava. X-ray films of the chest confirmed the impression of an intrathoracic neoplasm.

On July 30, 1923, anesthesia over the sensory field of the left fifth nerve was discovered. The left pupil was smaller than the right and the left lid slit was also reduced. The patient complained of a sense of numbness over the entire left side of the body but actual anesthesia could not be demonstrated. Pressure on the lumbar spine elicited tenderness. The patient finally died of asphyxia.

Post-mortem examination revealed a tumor of the right lung. There were in addition invasion of the pulmonary veins, metastases to the hilar lymph nodes, cervical glands, mediastinum, adrenals, pancreas, skull and brain.

There was one mass at the base of the brain which had eroded the base of the skull, and had pushed into the sphenoid, ethmoid and maxillary sinuses. It seemed to arise in the left temporal lobe, occupying most of this structure. The lateral ventricle was collapsed, the third ventricle was pushed to the right and the left internal capsule was pressed upon. This was the only metastatic mass in the central nervous system.

J. B., colored, male, 40 years of age. Johns Hopkins Hospital U-51771. Admitted September 8, 1924. Died September 20, 1924. The patient came to the hospital with a story of a sudden onset of nausea and vomiting which had persisted for four weeks. Associated with this had been diplopia, headache, dizziness and abdominal pain.

Physical examination revealed evidences of a recent marked loss of weight. The pulse rate was 60 a minute and the temperature was normal. The neurological findings included mental sluggishness, drowsiness, stiffness of the neck and slurred speech. An external squint was observed, but it could not be analyzed. The patient complained of numbness of the right hand, but no anesthesia could be demonstrated.

X-ray plates of the chest showed a spotty infiltration of both lower lung fields which was thought to indicate miliary tuberculosis. The spinal fluid contained 5 cells per cu. mm. and the protein was increased as shown by the Pandy test.

The patient's general condition grew worse and he became delirious. A neoplasm could not be ruled out, so ventriculography was done. The ventricles were enlarged but otherwise normal. The patient died 10 minutes later.

Necropsy demonstrated a primary carcinoma of the left lung which had metastasized to the bronchial nodes, lungs and kidneys. A mass about 2.5 cm. was found in the left frontal lobe. Scattered over the meninges, along the blood vessels at the base, and following the vessels into the sulci and into the substances of the

brain, were myriads of minute carcinoma deposits. It was a true carcinoma meningitis.

V. H., white, male, 48 years of age. Phipps Psychiatric Clinic and Johns Hopkins Hospital 5760. Admitted October 16, 1929. Died November 25, 1929. About four months before he was seen, the patient had had some fever, and noticed swelling of the hands and feet. There was an indefinite story of pain in the chest. A short time later, he had noticed that the tips of his fingers and toes were enlarged. One month before his hospital admission pain developed over the right eye followed shortly by diplopia and ptosis of the right lid. A generalized headache developed, and about two weeks later a non-productive cough and hoarseness were noted.

Physical examination showed a complete ophthalmoplegia of the right eye. Atrophy of the right side of the tongue was evident. The right lower leg was weak and spastic, and ankle clonus was obtained. Speech was indistinct but not aphasic. The ophthalmologist described slight blurring of the margins of the optic discs.

Laboratory studies added nothing. A roentgenograph of the chest showed a mass in the left upper lung field. The spinal fluid pressure was recorded as "normal." It contained 2 cells per cu. mm. but the Pandy reaction was negative.

The patient grew excited and delirious, then he became weaker and finally died in coma.

Autopsy revealed a carcinoma of the left upper lobe of the lung. Tumor deposits were found in the left kidney, adrenals, mediastinal lymph nodes, and skull. One metastasis was under the sella turcica and another was in the right sphenoidal fissure. A large cystic mass occupied much of the left anterior cerebral hemisphere.

M. S., colored, male, 45 years of age. Johns Hopkins Hospital U-24603. Admitted September 13, 1909. Died October 22, 1909. The patient came to the hospital with a complaint of headache for the previous eight months. For four months bouts of vomiting had occurred, followed by failing vision. His eyesight had grown progressively worse so that he had been totally blind for three weeks.

Examination revealed signs of recent weight loss. The patient was having visual and auditory hallucinations. The optic nerve heads were atrophic due to an old papilledema. The tendon reflexes were hyperactive and a positive Babinski response was noted on the right. During his hospital stay, restless movements of choreic type were prominent.

A decompression was done without relief. The patient died after having been stuporous for several weeks. A carcinoma of the lung was found at autopsy. Innumerable cysts ranging in size from a few millimeters to 2 centimeters in diameter, were found over the cortex and about the base of the brain. On section, many more were seen in the hemispheres and cerebellum. The cysts were full of

mucoid material. Microscopic sections demonstrated that the cysts were metastases from adenocarcinoma of the lung.

(C) Cases Characterized by Stupor

In six cases, the chief symptom was stupor and focal signs were absent or so doubtful that they were not considered important. In only one case was there evidence of increased intracranial pressure. It is of interest that the process in the lungs was silent clinically in all of these cases and that the correct diagnosis was never made. In three cases epidemic encephalitis or drug poisoning was suspected. The diagnosis of primary tumor of the brain was made in the remaining three cases.

E. H., colored, male, 32 years of age. Baltimore City Hospitals 6969. Admitted October 26, 1920. Died October 29, 1920. Eight weeks before admission the patient developed bronchitis which was accompanied by fever, anorexia, malaise and fatigue. A slight non-productive cough developed after this episode. These symptoms cleared rapidly but two weeks later the patient complained of generalized pain. Soon after this the patient became disoriented and on three occasions he tried to commit suicide. He was admitted to the hospital because of increasing stupor.

Physical examination disclosed a poorly developed and poorly nourished colored man who was quite stuporous. He mumbled incoherently, and his mouth hung open. Thorough physical and neurological examination by several members of the staff disclosed only dilated pupils, slightly exaggerated tendon reflexes and mild spasticity of the extremities.

Laboratory studies disclosed no abnormalities of the blood or urine. The blood Wassermann reaction was negative. A lumbar puncture disclosed an estimated normal pressure and clear fluid containing 3 cells per cubic mm. The Pandy and Wassermann reactions were negative. The gold curve was 0000000000.

The temperature on admission was 98.6 degrees F. It soon rose to 101°F., and the patient sank into coma and died. The clinical diagnosis was lethargic encephalitis.

Necropsy (1737) disclosed a solid tumor 10 x 40 cm. completely plugging the bronchus to the left lower lobe. Metastases were present in all other lobes of both lungs, in many hilar glands, liver, kidneys and adrenals. Several circular, pinkish masses about 1 to 2 cm. in diameter were found growing out of the dura. A small nodule 0.5 cm. in diameter was found in the right parietal lobe just posterior to the post-central convolution. The mass was in the cortex but under the pia. Microscopic examinations disclosed that all three masses were metastases from the carcinoma of the lung.

A. S., colored, female, 50 years of age. Baltimore City Hospitals 20893. Admitted February 6, 1937. Died February 14, 1937. The illness began three weeks

before admission with a severe headache. For several days there had been pain in the left side of the head and occasional attacks of vomiting. The patient was stuporous and incoherent on admission.

The physical examination showed the temperature to be 100°F., pulse 78, respirations 16 and blood pressure 160/100. The patient was drowsy, and complained of headache. The head was tender to percussion. Otherwise the physical examination was entirely negative. The neurological examination disclosed equal and regular pupils which did not react to light. The discs were normal and the fields could not be tested. The ocular movements were normal. The other cranial nerves were intact. There was no weakness of the extremities. Apraxia of the right arm was noted. No gross sensory changes were demonstrated. All the tendon reflexes were brisk. A Hoffman reflex was present on the right, but there was no ankle clonus or extensor plantar response.

Laboratory studies showed normal urine. The blood contained 4.38 million red cells, 10,700 white cells per cu. mm. and 11.3 grams of hemoglobin per 100 cc. The Wassermann reaction was negative. Blood chemistry determinations showed the non-protein nitrogen to be 30 and blood sugar to be 146 mgm. per cent respectively. The spinal fluid pressure was 300 millimeters of water. The fluid was clear and contained 6 cells per cu. mm. The Pandy reaction was faintly positive. The Wassermann reaction was negative. X-rays of the skull were negative. A chest plate was not taken.

The clinical impression was drug poisoning or encephalitis.

The patient remained stuporous, rapidly became weaker and died one week after admission.

Necrospy (7297) disclosed a scarred calcified area in the right lower lobe of the lung, 2 cm. in diameter, which was thought to be tuberculous. The brain was swollen and the convolutions flattened. In the right cerebellar hemisphere there was a large thin walled cyst which ruptured during removal of the brain. The third ventricle was tremendously dilated and the floor was ruptured as the brain was lifted up. A deep pressure cone was present in the cerebellum.

The cavity in the right cerebellar hemisphere was 2 x 4 cm., and in the wall was a nodule 1 x 2 cm. All the ventricles and the aqueduct of Sylvius were dilated. The medulla was distorted by pressure. Microscopic studies demonstrated that the mass in the lung was an adenocarcinoma with metastases to the hilar lymph nodes and in the right cerebellum.

W. L., colored, male, 45 years of age. Johns Hopkins Hospital 135030. Admitted February 23, 1939. Died February 28, 1939. The patient had been drowsy for three months, but he was able to work until six weeks before admission to the hospital. However, he would fall asleep at meals and was difficult to awaken. There had been no weakness, staggering or headache until four weeks before admission when he complained of bifrontal headaches and became very drowsy. For 48 hours previous to admission he had been comatose and incontinent.

Physical examination: Temperature, pulse and respiration were normal. The blood pressure was 100/20. There was evidence of moderate weight loss. The

patient could be aroused only by painful stimuli. The pupils were fixed to light in mid-position. A possible right central facial palsy was noted. The right arm was thought to be slightly spastic. Tendon reflexes were exaggerated in both arms but diminished in the legs.

The blood and urine were normal. Blood chemistry studies found the non-protein nitrogen to be 41 mgm. per cent, sugar 83 mgm. per cent, and the CO_2 combining power 57.0 vols. per cent. Lumbar puncture: The pressure was 60 mm. of water, 30 lymphocytes were present per cu. mm. Pandy and Wassermann reactions were negative. The mastic curve was 2221000000. No chest plates were taken.

The clinical impression was that a brain tumor was present. A ventriculogram was done and 100 cc. of air were injected. The lateral ventricles were markedly enlarged. An irregular defect was demonstrated in the posterior wall of the third ventricle, and an inoperable tumor of the third ventricle was suspected. The patient died three days later.

At autopsy a carcinoma of the bronchus (right upper lobe) was demonstrated with metastases to regional nodes, the right adrenal and brain. Sections of the brain at the level of the mammillary bodies on the right side showed a cystic tumor 3.5 cm. in diameter which pushed up the right internal capsule and pushed the third ventricle to the left. It extended anteriorly into the frontal lobe and posteriorly into the brain stem and pons to fill the aqueduct. Other masses in the left temporal lobe, right parietal lobe and left occipital lobe were found. These were each about 4 cm. in diameter.

J. D., white, male, of undetermined age. Johns Hopkins Hospital, 116875. Admitted September 10, 1937. Died September 18, 1937. Four years before admission the patient experienced a typical attack of angina pectoris. Following this he was well until four weeks prior to his hospital entrance when he developed a slight cough. This had become more severe and he went to bed. Generalized headache and difficulty with urination appeared at the same time. For one week aphasia and loss of memory had been prominent symptoms.

Physical examination on admission found the patient semicomatose. There was bilateral papilledema, 3–4 diopters. Tendon reflexes on the right were reduced.

Blood studies were normal and the blood Wassermann reaction was negative. No X-rays were taken of the chest. Roentgenogram of the skull showed a calcified pineal gland pushed down and backward.

Operation was performed and a large flap was turned down in the left frontal region. A cyst was found in the left frontal lobe. Thick, purulent material was aspirated and the lobe was excised. Another mass was found posteriorly in the Rolandic area, and was partially excised.

Following operation the patient went down hill and died.

At necropsy an "oat cell" carcinoma in the right lung was found. The mass filled the pulmonary veins and projected into both auricles of the heart. Metastases to the left lung and brain were demonstrated.

Large tumor masses were located in the left frontal and parietal lobes producing a collapse of the right ventricle. Other nodules were present in the right cortex at the level of the optic chiasm, and in the right side of the pons. Several small gelatinous masses were situated over the right cerebral hemisphere.

A. U., white, female, 57 years of age. Johns Hopkins Hospital U-74098. Admitted August 17, 1936. Died August 21, 1936. The patient came to the hospital in a deep stupor which had developed abruptly and without apparent cause four days before admission. It was related by the family that the patient had been told that she had hypertension six years previously. For the past three months, complaints of diplopia and headache had been mentioned.

Thorough physical and neurological examinations revealed very little except for the obvious stupor. The blood pressure was 150–90. The right pupil was slightly larger than the left, and some engorgement of the retinal veins was described.

Laboratory studies added little. The cellular elements and chemistry of the blood were normal. A trace of albumin was present in the urine. The serologic tests for syphilis were negative. X-rays of the chest were read as normal. A ventriculogram failed to demonstrate an intracranial neoplasm.

The patient died without regaining consciousness.

Post-mortem examination revealed a carcinoma of the right lower lobe of the lung, so small that it was overlooked the first time the lungs were sectioned. Metastatic deposits were present in the bronchial and trachial lymph nodes, in both adrenals, and over the peritoneum. The entire brain, pineal body and hypophysis were infiltrated by numerous small carcinomatous masses. The metastases were found on microscopic examination of the tissues, and because the cells resembled those of a carcinoma of the lung, the lungs were reëxamined and the small primary neoplasm was discovered.

A. L., colored, male, 58 years old, Baltimore City Hospitals 65177. Admitted: April 12, 1941. Died three hours later. The patient was stuporous on arrival at the hospital. He had had a cough for about three years. One month before admission, he complained of pain in the back, and generalized weakness. Three days before he was seen, edema of the ankles appeared. Shortly after this, he became delirious. This was followed by stupor which persisted until he was brought to the hospital.

Physical examination showed generalized anasarca and moderate dyspnea. Despite the edema, there was evidence of a considerable loss of weight. The trachea was deviated to the right and the entire left chest was dull to percussion. Breath sounds were transmitted poorly, and coarse bubbling rales were heard throughout both chests. The heart borders could not be determined by percussion. Sounds were distant and there was a gallop rhythm. The liver edge was 12 to 14 cm. below the costal margin. Marked edema of the abdomen and legs was present. The neurological examination was essentially negative. The

fundi were not visualized. The tendon reflexes were sluggish but equal on the two sides.

Except for a moderate anemia and a positive blood Wassermann reaction, the laboratory studies were negative.

The patient died three hours later before roentgenograms could be made. A post-mortem cisternal puncture revealed clear, spinal fluid free from cells. The Wassermann reaction was negative. The clinical impression was cardiac failure due to arteriosclerosis.

Necropsy (9981) revealed a bronchogenic carcinoma of the left upper lobe. Metastases were found in both lungs, both pleura, hilar nodes, liver, pancreas, adrenal, kidney, vertebra, thyroid and ribs. The skull was filled with metastases. The dura was covered by masses of tumor. One nodule about 12 mm. in diameter was found in the hypophyseal stalk. This extended into the hypothalmus and pressed into the floor of the third ventricle. A second metastasis about 5 cm. in diameter was located in the left occipital pole.

(D) Cases Characterized by Deposits in the Brain and Spinal Cord

In only one case in our series were there evidences of lesions in both the brain and spinal cord. It was a very puzzling case to the clinicans and many diagnoses were made before an autopsy disclosed the true state of affairs. The patient was thought to have central nervous system syphilis, a cord tumor and a gumma of the brain at various stages of his hospital admissions.

J. H. C., white, male, 53 years of age. Baltimore City Hospitals 39966. Admitted December 14, 1938. Died January 20, 1939. The patient had been first seen in the Neurological Dispensary of the Johns Hopkins Hospital on September 20, 1938 (unit number 153151) because of urinary incontinence. Three years before that he had had several attacks of numbness which radiated down his left thigh to the toes. During February, 1938, he was unable to walk for a short time, and the numbness became quite intense, soon changing to a dull ache in the left hip and back. Shortly afterward, constipation became bothersome, to be followed by a marked diminution of the size and strength of the urinary stream. Urinary frequency, loss of libido, semi-flaccid erections and loss of ejaculations were noted. By June, 1938, complete urinary incontinence developed, and the patient was no longer aware when urine was being passed. One month later suprapubic pain caused considerable distress. From February to September 1938 he had lost 15 lbs. in weight.

Physical examination in September, 1938 disclosed a chronically ill, poorly developed individual whose temperature, pulse and respiration were normal and whose blood pressure was 118/76. He was incontinent of feces and the anal sphincter was markedly relaxed. The prostate was only very slightly enlarged. Neurological examination disclosed unequal pupils, the left being larger than the

right. There was loss of touch and sharp-dull discrimination in the legs. The left knee reflex was increased but both Achilles reflexes were absent. Cystoscopic studies demonstrated a "neurologic bladder."

He was admitted to the urological service of the Johns Hopkins Hospital on October 18, 1938 because of albuminuria and pyuria. This cleared up rapidly. The blood Wassermann reaction was negative, and an X-ray of the chest showed pleural thickening at both apices, suggestive of old tuberculosis. The cerebrospinal fluid contained 138 cells per cu. mm. (90 per cent polymorphonuclear leucocytes), a 4 + Pandy reaction, 150 mgm. of protein per 100 cc. of fluid and a positive Wassermann reaction. The colloidal gold curve was 34443211000. Another lumbar puncture was done 6 days later and at this time the Pandy reaction was negative, and the protein was within normal limits but the Wassermann reaction remained positive. It was thought that all the symptoms could not be accounted for by central nervous system syphilis so two lipiodol injections into the dural canal were carried out. These failed to show any block.

The patient was discharged and received five injections of bismuth in the outpatient department.

Five days before admission to the Baltimore City Hospitals on December 12, 1938, his right eyelid had begun to droop and diplopia appeared. The right hand and arm became quite weak, followed by weakness of both legs. For one day he had felt very dizzy and was unable to walk. At this time, he related that five months previously he had suddenly become hoarse and lost his voice. The latter had returned slowly.

Physical examination at this time again showed a normal temperature, pulse and respiration, with a blood pressure of 100/58. Some hard, matted, slightly tender glands were felt in the axillae, which seemed fixed to the deeper structures. A gland was palpated in the supraclavicular region. The trachea was deviated slightly to the right but no tug was felt. The lungs were clear on percussion and auscultation. Neurological examination revealed unequal pupils, the right being larger than the left and both being irregular. Pupillary reflexes were sluggish. The visual fields and fundi were normal. A third nerve palsy was present on the right. There was weakness, atrophy and fasciculations of the right arm and hand. The other extremities showed increased tone. Saddle anesthesia was present (S4 and 5) and there was loss of touch over the area supplied by S2 and 3. Tendon reflexes were exaggeraged on the left. A Hoffman sign was present on the left, and there was a bilateral extensor plantar response. A diagnosis of meningovascular syphilis was made.

The urine contained many white cells. The blood contained 4.6 million red cells and 14,450 white cells per cu. mm. and 12.4 grams of hemoglobin per 100 cc. The Wassermann reaction was negative. The cerebrospinal fluid had a pressure of 75 mm. of water. It was clear but it contained 23 mononuclear cells per cu. mm. The Pandy was positive but the Wassermann reaction was negative. X-rays of the chest, spine and skull were read as normal.

While in the hospital, he received 9 injections of neoarsphenamine. He de-

veloped a decubitus ulcer. On January 20, 1939 he suddenly went into shock. The heart sounds were rapid and the pulse barely perceptible. Respirations ceased in about twenty minutes.

At autopsy (8632) a very small bronchogenic carcinoma was found in the left lung. Metastases had occurred to the hilar glands, lymph glands about the aorta, to the liver and both adrenals. Tumor was also found in the axillary, supraclavicular, pelvic and inguinal lymph glands. In the dura of the lower spinal cord there was a plaque about 2.5 cm. in diameter, surrounded by many small nodules. A nodule 3.5 cm. in diameter was found in the left temporal lobe, involving the hippocampus and choroid plexus. Another about 8 mm. in diameter was present in the centrum ovale. A third was present in the right occipital lobe and a fourth in the right Island of Reil. Two other masses were present in the anterior portion of the corpus callosum. Several small nodules were scattered over the meninges.

(E) Cases in Which the Cerebral Metastases Were Silent

In four cases there were cerebral lesions which failed to give rise to recognizable signs or symptoms. The deposits in one case involved the infundibulum and anterior lobe of the hypophysis and no doubt caused metabolic disorders which were overlooked. In another there were deposits in the occipital and parietal lobes, and, in the third, a single nodule in the right frontal lobe of the brain. In most cases the clinical picture was dominated by the process in the lungs and no special investigations of the nervous system were made. The diagnosis was correctly made once; in another case, it was recognized that the patient had malignant deposits in the lung but they were attributed to sarcoma of an undescended testis, and in the third case tuberculosis was suspected.

C. W., colored, male, 40 years of age. Baltimore City Hospitals Tuberculosis Division 5010. Admitted December 31, 1934. Died January 9, 1935. Three months before admission the patient contracted a "heavy cold" and cough. For the next two months he had many night sweats, and frequent attacks of nausea and vomiting. He became quite weak and lost 18 pounds. For one month he had a feeling of tightness under the sternum. Sudden hoarseness developed two weeks before hospital admission. There had never been any pain or hemoptysis.

Physical examination revealed a normal temperature, pulse and respiration. Blood pressure was 118/78. There was evidence of recent weight loss. The left chest moved poorly on respiration and tactile fremitus was absent. There was clubbing of the fingers. The neurological examination was negative.

The clinical impression was that a left pleural effusion was present. Laboratory studies revealed normal urine. The blood contained 2.71 million red cells

and 4770 white cells per cu. mm. The blood Wassermann reaction was negative. Several sputum specimens and pleural fluid examinations failed to demonstrate acid-fast bacilli. X-rays of the chest showed the entire left lung field obscured by fluid. An early tuberculous infiltration was described in the right upper lobe.

The patient steadily lost ground and died 10 days after admission.

At post-mortem (5946) a tumor 7 cm. in diameter was found projecting from the left main bronchus. Several cystic, necrotic metastases were found throughout the left lung, in the hilar glands and in both adrenal glands. The brain was normal, but much of the hypophyseal stalk and anterior lobe were replaced by tumor metastases. Microscopic sections established the diagnosis of bronchogenic carcinoma.

J. E. B., white, male, 50 years of age. Johns Hopkins Hospital U-50537. Admitted October 22, 1923. Died January 21, 1924. The patient was admitted to the hospital with a history of pain in the chest and back and hemoptysis of four weeks' duration.

Examination showed signs of fluid and consolidation at the left lung base. The left testis was absent. The neurological examination was negative. Laboratory studies added nothing and a sarcoma of an undescended testis was suspected.

The patient grew slowly weaker and died without developing any new signs. Autopsy disclosed carcinoma of the left lung, which had metastasized to the liver, adrenals, and kidneys. A small tumor nodule was present in the right frontal lobe of the brain.

L. C. H., white, female, 51 years of age. Johns Hopkins Hospital U-59033. Admitted November 10, 1934. Died February 9, 1935. For one month the patient had been bothered by abdominal pain, nausea and vomiting. She had been a drug addict for years and under treatment since 1910. Optic atrophy and polyneuritis had been present for many years, and it was thought that alcohol or drugs were responsible.

Physical examination revealed dullness to percussion over the left upper lung, without changes in the breath sounds; no râles were heard. A mild, diffuse abdominal tenderness was present. The optic discs were pale. The ankle and knee jerks were absent.

X-ray studies demonstrated a shadow at the left lung root. At operation a carcinoma was found, but it could not be removed.

X-ray therapy was given without benefit. On January 9, 1935, while receiving intravenous glucose, the patient developed a transient facial palsy, difficulty in speech and mental confusion. These disappeared after a few hours. Following this the patient steadily lost ground, and died one month later.

Autospy revealed an extensive carcinoma of the left lung. There were two intracranial deposits, one in the dura compressing the right parietal lobe, and one in the substance of the left occipital lobe.

W. H., white, male, 54 years of age. Baltimore City Hospitals 60120. Admitted April 20, 1940. Died February 26, 1941. The patient was brought to the hospital in an alcoholic coma. When he had revived, a history was obtained of cough, with purulent sputum, which had developed about four months previously. Shortly after this, he experienced precordial pain, exertional dyspnea, and hoarseness.

Physical examination revealed a chronically ill patient. He was very hoarse and there was complete paralysis of the left vocal cord. The percussion note was impaired at both apices, and many rales were heard at the right apex. The breath sounds were distant in the left axilla. The heart was moderately enlarged but the blood pressure was only 120/60.

Neurological examination revealed moderate atrophy of the small muscles of the left hand, and fasciculations were noted in the muscles of the forearms. The tendon reflexes were diminished in the left arm. There were no sensory changes, and the cranial nerves were intact.

X-rays of the chest demonstrated clouding at the left apex and in the right mid-lung region. This was interpreted as tuberculosis. Blood and urine studies were negative. The cerebrospinal fluid pressure was 150 mm. of H_2O and the dynamics normal. The fluid was clear and it contained 4 cells per cu. mm. The Pandy and Wassermann reactions were negative. Sputum studies failed to reveal acid-fast bacteria.

While the patient was in the hospital he complained of pain in the left chest. After extensive studies he was transferred to the Infirmary where he complained of loss of weight and appetite and epigastric pain. A gastrointestinal series was reported as normal.

On December 24, 1940, it was noticed that he had become jaundiced. Upon readmission to the hospital it was found that he had lost about 50 pounds in weight. Examination at this time showed no change in the chest or laryngeal findings. However, many hard, fixed glands could be felt in the left cervical region, both axillae and in the left inguinal region. One of these glands was removed and it was found to contain adenocarcinoma, which the pathologists suggested might be derived from a lung or stomach neoplasm.

X-ray of the chest was said to show old healed tuberculosis of the left upper lung. This had remained unchanged in several plates taken during this hospital stay.

The jaundice became intense. The patient lost ground steadily and died of exhaustion. The clinical diagnosis was carcinoma of the head of the pancreas.

Post-mortem examination (9696) revealed a bronchogenic carcinoma arising in the left upper lobe of the lung. Metastases to the cervical, periaortic, axillary and inguinal glands were demonstrated. A large tumor mass was present in the pancreas, causing obstruction of the bile ducts. One metastatic nodule, 0.5 cm. in diameter was found in the left thalamus. It was not pressing upon the internal capsule.

(F) Cases in Which the Spinal Cord Alone Was Involved

In four cases the signs and symptoms were referable to the spinal cord alone. There was paraplegia in two due to lesions in the thoracic region. Tetraplegia due to compression of the cord above the cervical enlargement was present in another case and, in the fourth case, the roots of the cauda equina were involved, causing sacral anesthesia and incontinence. The neurological picture was that of a single lesion in each case probably because the highest lesion masked the presence of lesions below. The Queckenstedt test was positive in two cases, negative in one, and was not performed in the fourth one. Roentgenograms of the spine were made in two cases. In one, metastatic deposits were discovered in the vertebrae, and in the other nothing abnormal could be demonstrated. The correct diagnosis was made twice, due to recognition of the lesion in the lungs, and twice primary tumor of the spinal cord was suspected.

J. G., white, male, 60 years of age. Johns Hopkins Hospital 32172. Admitted July 15, 1930. Died July 20, 1930. Four months before admission a non-productive hacking cough had appeared followed by sharp pain in the right chest. An X-ray of the chest was taken in the Out-Patient Department and a diagnosis of pleurisy at the right lung base was made. Two weeks before admission the patient began to experience weakness of the legs and by five days before entry to the hospital he was unable to stand.

Physical examination disclosed a small nodule over the right parietal region of the skull. Percussion demonstrated dullness over the right lower chest. Breath sounds were absent over the same region. The biceps and patellar reflexes were exaggerated on both sides. The abdominal reflexes were absent. Bilateral Babinski responses were present. Neither a Hoffman reflex nor ankle clonus could be obtained. Paresthesia and hyperesthesia were present below the right knee. Involuntary jerking of the right leg was noted.

Thoracentesis produced no fluid. Lumbar puncture showed a pressure of 140 mm. H_2O. The fluid contained no cells, but there was a faintly positive Pandy reaction. A Queckenstedt test was not done.

The patient died suddenly several days later.

Postmortem examination revealed a primary carcinoma of the right lung with extension into the pleura and pericardium. Metastases were found in the sternum, spine, adrenals, kidneys, liver and mesenteric lymph nodes. A nodule was discovered in the right temporal lobe of the brain. The spinal cord was not properly studied.

F. D., white, male, 58 years of age. Johns Hopkins Hospital U-65982. Admitted July 3, 1936. Died July 5, 1936. The patient had complained of precordial pain for seven months to which was added pain in the neck and shoulders of two months' duration. Weakness of the left arm had been noted for two weeks previous to admission, followed by paralysis of the arms and legs and retention of urine for five days.

General physical examination was negative. Neurological examination revealed a flaccid tetraplegia. A sensory level was present at about C5. The tendon reflexes were absent and pathological reflexes were not obtained. The patient's temperature rose to 104 degrees F. and he died two days after admission, before any detailed studies could be carried out.

Necropsy demonstrated a bronchogenic carcinoma in the lower lobe of the left lung. Tumor deposits were found in the heart, spleen, seventh rib, and cervical and axillary nodes. The spinal cord was compressed and flattened in the lower cervical region. A small hemorrhage was described in the medulla, but no tumor cells were seen.

H. F., white, male, 53 years of age. Johns Hopkins Hospital U-120084. Admitted September 9, 1937. Died September 25, 1937. The first symptoms, weakness, pain in the chest and loss of weight, developed six months before he was seen. Six days before admission his legs had suddenly become paralyzed.

The physical examination revealed extensive weight loss (40 pounds). There was dullness on percussion over both upper lung fields posteriorly. The neurologist reported a flaccid paraplegia of the legs, retention of urine and a sensory level at T5 or 6. All forms of sensation were lost below this level.

X-ray studies showed a mass in the upper lobe of the left lung, and collapse of the fifth thoracic vertebra. The spinal fluid was yellow and it contained a marked excess of protein (Fröin syndrome).

The patient went gradually down hill and died two weeks later. Autopsy confirmed the clinical impression of a bronchogenic carcinoma of the left lung. Metastases were found in the thyroid gland and in the brain. The fifth thoracic vertebra had collapsed. The cord was compressed and softened at this level.

It is interesting to note that although deposits of tumor were present in the brain, these were silent, and all the neurological signs were due to compression of the cord caused by the collapse of a vertebra.

W. M., white, male, 39 years of age. Johns Hopkins Hospital U-50834. Admitted August 18, 1933. Died August 29, 1933. The patient came to the hospital with the complaint of pain of eight weeks' duration in the lumbar region. The pain radiated down the back of the legs. Some loss of weight had been noted.

The physical examination was negative, except that the temperature was slightly elevated. The only neurological findings were absent ankle reflexes and an area of anesthesia over the left buttock.

Chest X-ray films showed fibroid infiltration of the right upper lung and enlargement of the mediastinal lymph nodes. These were interpreted as being due to tuberculosis. Roentgenograms of the lumbar spine revealed no abnormalities. The spinal fluid contained 7 cells per cu. mm. and an excess of protein. The Queckenstedt test showed a block in the subarachnoid space. Lipiodol introduced into the cistern showed an obstruction in the upper thoracic region.

A laminectomy was performed at T5, and a tumor was found lying on the dura. The patient died on the same day.

Postmortem examination revealed a carcinoma of the right lung. Metastases were found in several of the vertebrae, in the cervical and abdominal lymph nodes, adrenals, left lung and pleura. The tumor removed at operation was also a metastasis.

A minute carcinoma of the prostate was also found but this had not metastasized.

II. Analysis of Symptoms

There is nothing particularly characteristic about *focal signs* due to metastatic deposits in the brain of carcinoma of the lungs. As a rule, it may be said that they are relatively mild and incomplete. Thus, hemiparesis is more common than hemiplegia, and difficulty in speech more common than complete aphasia. The onset was rapid in most cases but if we may rely upon the histories, not so abrupt as that of symptoms due to vascular lesions. In one case, however, the onset of hemiparesis was so sudden as to suggest thrombosis of a cerebral artery and thus led to an incorrect diagnosis. One might suspect that in such cases we are dealing with embolism due to tumor cells in the blood stream. The same explanation might be offered in the cases in which a sudden convulsion is followed by hemiplegia or other focal sign.

In only five of the twenty-two cases in which there were cerebral deposits was there *papilledema*. In most of the others, there was complaint of headache, but headache alone cannot be taken as definite evidence of increased intracranial pressure. In ten cases, the spinal fluid pressure was estimated. In only three was it definitely above normal, readings of 300, 350 and 350 mm. of water being obtained. In all other cases, normal pressure readings were found. Thus, it may be concluded that increased intracranial pressure is not a frequent finding in this condition, and when it occurs, it does so in the late stages of the disease.

Cervical rigidity was observed in only one case. In this case, Kernig's sign was absent.

Convulsions marked the onset of neurological symptoms in four cases. Strangely enough convulsions never developed late in the course of the illness and were observed only in cases characterized by signs of a single focal lesion.

Mental disorders were seen in most cases in which deposits were found in the brain. As a rule, they were merely dullness, drowsiness and stupor deepening into coma, but in a few cases there were delirium and excitement. Hallucinations were prominent in two cases and suicide was attempted in another.

III. Laboratory Studies

In twelve of the twenty-two cases in which the brain was involved, the *spinal fluid* was carefully examined. In six cases the protein content was increased, ranging from 70 to 160 mgm. per cent. The cell count was increased in only two cases, in which counts of 20 and 30 lymphocytes per cu. mm. were discovered.

In all four of the cases in which the spinal cord was involved the protein was increased; in two of them a great excess of protein was present. In one case, in which there were both cerebral and spinal deposits a cell count of 138 per cu. mm. was found but since the Wassermann reaction was positive, the significance of this observation is doubtful.

Roentgenograms of the *skull* showed metastatic deposits in one case. In another there was displacement of the pineal shadow. In none of the other cases was this method of examination productive.

Roentgenograms of the spine were made in two cases in which there were symptoms referable to the spinal cord. In one, destructive lesions of the vertebrae were found and in the other no lesions were demonstrable.

Ventriculography was performed seven times. In two instances this procedure revealed no change in the size or shape of the ventricular system. In two cases, the lateral ventricles were symmetrically dilated. Once a mass was found in the right frontal lobe. In two instances a more typical condition was discovered, namely, irregularity of the ventricular outlines due to many small deposits under the

ependyma. It is evident, therefore, that ventriculography in this condition does not reveal uniform or characteristic changes in the ventricular system. Only once were multiple deformities in the ventricular outlines noted and their significance recognized before post-mortem examination.

The fact that ventriculograms may seem normal was commented upon by Dandy who remarked that each individual metastatic tumor may be too small to produce a local deformity in the ventricular system. Also the aggregate of many lesions may leave the ventricular system with nearly normal symmetry. This is particularly true in cases of lung tumors because the metastases tend to be small and multiple. It is only where there are one or two large nodules that ventriculography will demonstrate the intracranial neoplasms.

Lipiodol was injected twice when spinal cord tumors were suspected. In one case the test failed to reveal obstruction of the spinal canal; in the other, obstruction of the spinal subarachnoid space was demonstrated.

NON-NEUROLOGICAL FEATURES

The typical clinical symptoms are, of course, cough, loss of weight, hemoptysis and pain in the chest. In about half of our cases, physical signs of a mass in the lung were demonstrated. Pulmonary symptoms may be absent at a time when the neurological features are well advanced. In fourteen of our twenty-seven cases, the neurological symptoms were dominant and the pulmonary process may be said to have been silent. Loss of weight may be so slight as to escape attention, probably because of the rapid course of the disease. Even when the pulmonary symptoms are evident, it is often difficult to make the correct diagnosis. Thus, in our whole series of one hundred cases, in only sixty-four was the correct diagnosis of carcinoma of the lung made on clinical grounds. In five cases pneumonia was diagnosed, in two cases, lung abscess, in three cases pulmonary tuberculosis was diagnosed, and lymphosarcoma, carcinoma of the liver, and Hodgkin's disease were suggested in one case each. In the remaining cases the presence of a lesion in the lungs was not suspected. In two cases there were signs of a mass in the mediastinum indicating compression of the superior vena cava and once there was cardiac disturbance due to a deposit in the heart muscle.

SUMMARY AND CONCLUSIONS

As a result of the above study, we offer the following conclusions:

1. Carcinoma of the lungs causes about 0.5 per cent of all deaths.

2. It is a disease of middle age having its chief incidence between the ages of 40 and 60 years. It is more frequent in males than females, but our figures would seem to indicate that there is no significant difference between the incidence in whites and in Negroes.

3. Carcinoma of the lungs metastasizes to the brain very frequently and very early. In many instances, evidences of deposits in the brain appear before pulmonary symptoms.

4. Deposits in the brain are usually multiple and of relatively small size. They are scattered indiscriminately throughout the cortex, white matter, brain stem, hypothalamus, cerebellum and meninges. Less commonly, larger metastases are found which may reach a diameter of 4 cm. and are usually necrotic in the center.

5. The neurological syndromes which result from deposits in the nervous system may be classified as follows:

a) Cases in which the picture is consistent with a single focal lesion of the brain. These cases resemble primary neoplasms of the brain or vascular lesions.

b) Cases in which there are signs of multiple focal lesions in the brain. The diagnosis should be easier in these cases but they may be mistaken for primary intracranial neoplasms or vascular lesions.

c) Cases in which the presenting symptom is stupor without definite focal signs. These are usually mistaken for instances of epidemic encephalitis or drug poisoning.

d) Cases marked by multiple lesions in the brain and spinal cord.

e) Cases in which the spinal cord alone is involved. These are almost always confused with primary neoplasms of the cord.

6. Our analysis of the individual symptoms and signs has led to the following conclusions:

a) Focal signs are usually mild and incomplete. They are frequently of rapid onset and development and occur so abruptly as to suggest embolism, thrombosis or hemorrhage.

b) Not infrequently convulsions mark the onset of nervous symptoms and these are frequently followed by hemiplegia.

c) Headache is very frequent but papilledema is uncommon, being present in only five of our 27 cases.

d) Signs of meningeal irritation are rare.

e) Mental disturbances are very common but not characteristic. Drowsiness passing into stupor and coma is most frequently observed. Delirium and excitement are rare. Hallucinations were noted once and suicide was attempted by one patient.

f) The spinal fluid pressure is rarely elevated in our experience, but there is usually an excess of protein. When the spinal cord is involved Fröin's syndrome may occur.

g) Roentgenograms of the skull and bones rarely reveal metastases in patients with neurological signs. As a corollary, the bones may be riddled with metastases and at autopsy the brain will not be involved.

h) Ventriculography may reveal normal ventricles, dilated ventricles, signs of a mass within the cranium or multiple filling defects in the walls of the ventricles, a condition which is suggestive of metastases. In our experience, it is difficult to make a positive diagnosis of multiple tumors by this method.

i) The growth in the lungs may be silent at a time when the neurological symptoms are well advanced. In our series of 27 cases, the neurological features were predominant in 14.

j) If the process in the lung is detected it may be mistaken for tuberculosis, abscess of the lung, Hodgkin's disease, lymphosarcoma, etc.

k) Deposits in the kidneys and other viscera rarely give rise to any recognizable symptoms. The adrenal glands are affected in a high percentage of cases and it is possible that this may influence the clinical picture. Deposits in the hypothalamus and anterior lobe of the hypophysis may cause somnolence or stupor. Deposits in the skin or lymph nodes may be found in some cases and permit a correct diagnosis by biopsy.

7. In the light of the above statements, it seems wise to have a careful roentgenographic study made of the chest in the following conditions:

a) In all cases in which there is reason to suspect an intracranial neoplasm.

b) In all cases in which there is reason to suspect a spinal cord neoplasm.

c) In all cases of unexplained stupor.

BIBLIOGRAPHY

ALPERS, B. J., AND SMITH, O. N.: Carcinomatosis of the Meninges of the Spinal Cord and Those of the Brain without Involvement of the Parenchyma Secondary to Carcinoma of the Lung. *Am. J. Cancer*, **32:** 316, 1938.

CRAIG, W. McK., WOLTMAN, H. W., AND KERNOHAN, J. W.: Metastases to the Central Nervous System from Carcinoma of the Lung. *Am. J. Cancer.*, **36:** 12, 1939.

DANDY, W. E.: DEAN LEWIS, *Practice of Surgery*, vol. 12 (W. F. Prior Co.), 1940.

DAVIDSON, C., AND HORWITZ, W. A.: Primary Carcinoma of the Lungs with Metastasis to the Central Nervous System. *Arch. Int. Med.*, **46:** 680, 1930.

EWING, J.: *Neoplastic Disease* (W. B. Saunders Co.), 1940.

FRIED, B. M., AND BUCKLEY, R. C.: Primary Carcinoma of the Lungs in Intracranial Metastasis. *Arch. Path.*, **9:** 483, 1930.

GLOBUS, J. H., AND SELINSKY, H.: Metastatic Tumors of the Brain. *Arch. Neurol. & Psychiat.*, **17:** 481, 1927.

GRANT, F. C.: Concerning Intracranial Malignant Metastases. *Ann. Surgery*, **84:** 635, 1926.

HEINEMANN, J.: "Ueber die Metastasierung Malignes Tumoren ins Zentralnervensystem." *Virch. Arch.*, **205:** 418, 1911.

MORSE, M. E.: Two Cases Illustrating the Pathological and Psychiatric Aspects of Carcinomatous Metastasis in the Central Nervous System. *J. Nerv. & Ment. Dis.*, **58:** 409, 1923.

ROGER, H., CORNIL, L., AND PAILOON, J. E.: Anatomic and Pathogenic Study of Metastatic Cerebral Tumors. *Rev. Neurol.*, **72:** 137, 1939.

DIETARY PROTEIN AND THE REGENERATION OF SERUM ALBUMIN[1]

IV. The Potency Values of Dried Beef Serum, Whole Egg, Cow's Milk, Cow's Colostrum, Lactalbumin, and Wheat Gluten

A. A. WEECH

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York

Submitted for publication January 12, 1942

The fact that various food proteins differ qualitatively in their ability to promote the synthesis of serum protein has been established by observations at Rochester (1, 2, 3, 4, 5), at Yale (6, 7, 8), and in the laboratory of the author at Columbia (9, 10, 11). A review of work in this field has been published by Madden and Whipple (12). The technic of assay used at Rochester and at Yale has given information concerning the effect of various foods on the total protein of plasma. The method in use at Columbia has dealt restrictedly with factors responsible for the replenishment of the albumin fraction of serum. Previous papers have dealt with the "potency values" for albumin formation of fresh beef serum, egg white, beef muscle, beef liver, casein, and gelatin. The present communication will be concerned with the potency values of dried beef serum, whole egg, cow's milk, cow's colostrum, lactalbumin and wheat gluten. The relative effectiveness of each of these foods and of the foods previously reported on will be evaluated.

METHOD OF ASSAY

A complete description of the method of assay and of observations which led to establishing the method in its present form was given in an earlier publication (9). A healthy dog is selected and placed

[1] This investigation has received support from the Williams-Waterman Fund for the Combat of Dietary Diseases.

under daily observation for 6 days on a standard diet of adequate protein content. The standard diet is a mixture of 900 grams of a basal low protein diet (13), with 90 grams of casein. The concentration of albumin in the serum is then measured; the casein is removed from the diet and a period of depletion of the serum albumin is begun. After 3 weeks the serum is again analyzed for albumin and the period of regeneration is started on a diet composed of a mixture of the basal diet and the food protein to be tested. The mixture is fed in amounts which provide 80 calories and 2.5 grams of protein per kilo per day. After one week on this diet the final measurement of serum albumin concentration is made.

The initial albumin analysis is a control determination only and is not used in evaluating the assay. The *assay value* of a food is calculated as 0.15 plus the figure which represents, in grams per 100 cc., the rise in albumin concentration in the serum during the week in which the food was fed. The constant, 0.15, is to be regarded as an allowance for maintenance; it was determined from 23 control experiments in which during a fourth week of maintenance on the basal ration the decline in albumin in the serum averaged 0.15 grams per 100 cc. When assay values are determined for the same food on a number of different animals, the range of variation among the results will be fairly wide. It follows that a series of assays must be made before an average value or *potency value* can be assigned to the food protein.

EXPERIMENTAL FINDINGS

Dried Beef Serum. In previously published experiments (11) the protein of fresh beef serum was shown to be more effective in producing albumin synthesis than any of five other foods which had been studied. In conducting these assays it was necessary to prepare fresh serum by centrifuging defibrinated beef blood purchased at an abattoir. Centrifugation was slow and to obtain the amounts of serum needed for the diets large volumes of blood were handled. The final product could be preserved in the refrigerator for a limited number of days only. For these reasons and because it was hoped that a form of beef serum suitable for inclusion in human diets could be found, attention was directed to the effectiveness of dried beef serum.

Dried beef serum is available on the market as "light blood albumin"; the material is used commercially in the preparation of a coating for leather and textiles and in the manufacture of a water-resistant glue for veneering purposes. Light blood albumin was prepared in the following way for inclusion in the dog's ration: Approximately 100 grams were added slowly to a liter of water during continuous agitation by a mechanical mixer; the agitation was continued for 20 minutes to bring about solution. A small amount of insoluble residue was removed by centrifugation and the supernatant reconstituted serum placed in a double boiler and heated over a bunsen flame. After the contents had commenced to gel, it was stirred frequently until the coagulated protein began to separate from the serum whey. Longer cooking was found to render the curd rubbery and tough and was therefore avoided. The material was poured on a wire strainer and drained with gentle pressure to remove the whey. Finally the curd was centrifuged for 10 minutes to remove more of the whey and to bring the coagulum to an approximately constant degree of hydration. In this coagulated cooked form the serum protein was added to the diets. A number of batches were prepared and mixed together thoroughly before each set of experiments. The mixture was analyzed for nitrogen and preserved until needed in a tightly covered can at 4 degrees Centigrade.

Different lots of the mixed protein curd contained from 13.1 to 15.2 per cent protein (N $\times$ 6.25). The regeneration diet was a mixture of 53.4 grams of basal diet and 2.04 grams of serum protein per kilo of dog's weight per day. The amount of curd actually added to the diet varied with its protein content. In the diet as fed 81.8 per cent of the total dietary protein was furnished by the curd; the remainder represented the nitrogen content of the basal ration.

Eleven dogs were used in the experiments with light blood albumin. The results of the assays are given in Table I. The individual assay values vary between 0.55 and 0.93 and yield an average assay value or potency value of 0.739. Statistical test does not disclose that this value differs significantly from that of 0.801 found in eleven previously reported assays of fresh beef serum. Accordingly it is of some interest to combine the two series of experiments so as to obtain a

potency value based on a larger number of assays. This value, determined from eleven assays of dried serum and eleven assays of fresh serum, is 0.770.

Because light blood albumin is a product which could be marketed in a form suitable for human consumption, considerable effort was made to prepare the protein in ways which would render it palatable. Unfortunately a lingering and unpleasant flavor in the material at our disposal could not be eliminated and prevented the preparation

TABLE I

Assays of Dried Beef Serum for Albumin Formation

DOG	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
	Initial	Depletion	Regeneration	Loss	Gain	
	grams	*grams*	*grams*	*grams*	*gram*	
2-05	3.69	2.55	3.33	1.14	0.78	0.93
2-07	4.01	2.80	3.56	1.21	0.76	0.91
3-35	4.07	2.89	3.64	1.18	0.75	0.90
3-94	4.05	3.13	3.84	0.92	0.71	0.86
3-36	4.33	3.26	3.90	1.07	0.64	0.79
1-69	3.46	2.47	3.01	0.99	0.54	0.69
1-55*	3.83	3.16	3.62	0.67	0.46	0.68
3-08	3.95	2.54	3.03	1.41	0.49	0.64
2-14	3.66	2.59	3.05	1.07	0.46	0.61
3-93	3.81	2.61	3.03	1.20	0.42	0.57
7-31	3.59	2.69	3.09	0.90	0.40	0.55

Potency value: 0.739 ±0.029 (P.E.).

* In this experiment, because the loss in albumin concentration was relatively low, the regeneration period was terminated after 6 days. The assay value was calculated as seven sixths of the gain +0.15. Justification for this modification has been given in another place (9).

of dishes attractive to the human taste. Probably the distasteful feature can be overcome but it would seem that studies designed toward this objective must begin in the abattoir rather than in the assay laboratory.

Whole Egg. In previous experiments (11) the protein of egg white was shown to be highly effective in promoting the synthesis of serum albumin. For this reason and because of the importance of eggs in the American dietary, the potency value of whole egg was determined from a series of twelve additional assays. The effectiveness of

the yolk of egg, as apart from the white, has not been measured. The eggs were boiled for at least 20 minutes before removing the shells and chopping finely. The chopped egg was preserved in a tightly covered can at 4°C. until needed for inclusion in the diets. Numerous weighings showed an average composition of the eggs of 37 per cent yolk and 63 per cent white. Yolk and white were analyzed separately for nitrogen; the results, calculated as protein, showed: for the yolk, 15.7 per cent; for the white, 12.3 per cent. The

TABLE II

Assays of Whole Egg for Albumin Formation

DOG	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
	Initial	Depletion	Regeneration	Loss	Gain	
	grams	grams	grams	grams	grams	
3-94	4.47	3.21	3.93	1.26	0.72	0.87
6-93*	4.10	3.44	4.01	0.66	0.57	0.82
3-35	4.24	3.06	3.67	1.18	0.61	0.76
7-31	3.72	2.79	3.39	0.93	0.60	0.75
3-36	4.39	3.57	4.02	0.82	0.45	0.60
1-69	3.79	2.66	3.10	1.13	0.44	0.59
3-08	3.83	2.82	3.24	1.01	0.42	0.57
2-66	3.99	3.12	3.50	0.87	0.38	0.53
2-07	4.17	3.11	3.44	1.06	0.33	0.48
3-34	3.65	2.48	2.81	1.17	0.33	0.48
5-31	3.97	3.10	3.42	0.87	0.32	0.47
6-95*	3.82	3.21	3.34	0.61	0.13	0.30

Potency value: 0.602 ±0.033 (P.E.).

* The regeneration period was terminated after 6 days. The method of computing the assay value is given in the footnote to Table I.

fat content of the yolk was not determined; the figure, 33.3 per cent, used in computing the diets was taken from the tables of Atwater and Bryant (14). These data yielded a calculated composition for the chopped boiled whole egg of 13.6 per cent protein and 12.3 per cent fat. The components of the regeneration diet in terms of amount fed per kilo per day were: for the basal diet, 39.37 grams; for the whole egg, 15.96 grams. With this mixture 86.6 per cent of the total protein of the diet was furnished by the egg.

The data dealing with the twelve assays of whole egg are sum-

marized in Table II. The separate assay values cover a range from 0.30 to 0.87 and yield an average or potency value of 0.602. This figure is almost identical with that of 0.616 obtained in eleven previously reported assays of egg white. The result suggests that the proteins of the two fractions of egg may be of equal value in promoting the synthesis of serum albumin. Combining the two sets of assays results in a potency value of 0.608 for egg protein as a whole.

Cow's Milk. In all of the eleven experiments with milk the animals tended to have large pale foul-smelling stools. In the attempt to eliminate this objectionable feature several types of milk were used, that is, five of the assays were performed with fresh whole milk, three were carried out with a dried half-skimmed milk (Dryco), and three were conducted with a commercial brand of dried skimmed milk containing only 0.1 per cent fat in the reconstituted state. Analyses for protein were made on each type of milk. The figures for fat and carbohydrate content used in the calculation of energy values were those given by the manufacturer or, in the case of fresh milk, furnished by the dairy. The proportion of the total dietary protein furnished by milk protein was: for fresh whole milk, 90 per cent; for Dryco, 87 per cent, and for skimmed dried milk, 85 per cent.

The results of the assays of milk are presented in Table III. The assay values range from 0.35 to 0.68 and yield an average or potency value of 0.483. There is no indication in the results that one type of milk is superior to another in promoting albumin synthesis.

Cow's Colostrum. The colostrum from cows immediately after calving is listed by Rogers (15) as containing 17.6 per cent protein. Approximately one third of this protein is casein; the remaining two thirds is made up of a little albumin and much globulin. Crowther and Raistrick (16) have shown that colostrum globulin is identical with serum globulin; the finding has been confirmed in anaphylactic tests by Wells and Osborne (17). For this reason the thought was entertained that this concentrated protein food might possess a potency value for albumin synthesis like that of beef serum.

All of the colostrum used in these experiments was collected within 6 hours of the time of calving. Each shipment to the laboratory represented the combined output of from three to five cows. Six

shipments were required to complete the assays. Each lot was analyzed as soon as received for protein and fat; lactose was not determined, the figure 2.19 per cent, given by Rogers (15) being used throughout in computing the composition of the regeneration diet. The protein content (N × 6.25) of the six samples of colostrum varied from 12.6 to 16.4 per cent and averaged 15.2 per cent; the fat content ranged from 3.5 to 5.2 per cent and averaged 4.7 per cent. The relative amounts of colostrum and basal ration making up the regeneration diet were computed separately for each shipment of colos-

TABLE III

Assays of Cow's Milk for Albumin Formation

DOG	TYPE OF MILK	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
		Initial	Depletion	Regeneration	Loss	Gain	
		grams	grams	grams	grams	grams	
3-94	Fresh	4.30	3.50	4.03	0.80	0.53	0.68
2-66	Dryco	4.08	2.93	3.36	1.15	0.43	0.58
1-69	Dry Skim	3.69	2.40	2.82	1.29	0.42	0.57
3-36	Dryco	4.28	3.35	3.75	0.93	0.40	0.55
7-31	Dryco	3.67	2.73	3.06	0.94	0.33	0.48
3-34	Dry Skim	3.72	2.36	2.69	1.36	0.33	0.48
3-35	Fresh	4.00	2.99	3.27	0.73	0.28	0.43
2-14	Fresh	3.70	3.03	3.31	0.67	0.28	0.43
3-93	Fresh	3.91	3.22	3.46	0.69	0.24	0.39
3-08	Fresh	3.61	2.85	3.07	0.76	0.22	0.37
6-48	Dry Skim	3.34	2.62	2.82	0.72	0.20	0.35

Potency value: 0.483 ±0.021 (P.E.).

trum. Actually the fraction of total dietary protein furnished by colostrum varied only from 83.2 to 84.1 per cent.

The results of the nine experiments with colostrum milk are presented in Table IV. The assay values range from 0.36 to 0.84 and yield an average or potency value of 0.611. The effectiveness is about what would be expected if colostrum protein were a mixture of the proteins of milk and serum.

Lactalbumin. Comparison of the potency values obtained in assaying casein and the mixed proteins of whole milk suggested that the whey protein of milk might be the agent responsible for the somewhat

greater effectiveness of whole milk. Accordingly a series of assays of lactalbumin was undertaken. In the first twelve experiments the lactalbumin was obtained from the Borden Company; it was the type marketed as Labco Lactalbumin 15–42. Because of a probable error in interpreting the results of our analyses of this product, the data from the assays will not be given in detail. They do, however, possess some value in supporting the findings in a later series of experiments. For the purpose of analysis the lactalbumin was dissolved in a dilute solution of sodium hydroxide. The solution was analyzed in the same way as are samples of serum, that is, protein

TABLE IV

Assays of Cow's Colostrum for Albumin Formation

DOG	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
	Initial	Depletion	Regeneration	Loss	Gain	
	grams	*grams*	*grams*	*grams*	*gram*	
6-49	3.96	2.35	3.04	1.61	0.69	0.84
1-69	4.19	2.81	3.49	1.38	0.68	0.83
3-94	4.45	3.11	3.70	1.34	0.59	0.74
5-31	3.27	2.35	2.89	0.92	0.54	0.69
3-08	3.93	2.79	3.29	1.14	0.50	0.65
2-07	3.99	2.98	3.42	1.01	0.44	0.59
3-35	3.82	3.18	3.47	0.64	0.29	0.44
3-93	4.00	3.19	3.40	0.81	0.21	0.36
7-31	3.54	2.76	2.97	0.78	0.21	0.36

Potency value: 0.611 ±0.042 (P.E.).

nitrogen was taken to be the difference between total nitrogen and the nitrogen moiety remaining in solution after precipitation of protein with tungstic acid. On this basis two shipments of the lactalbumin showed 64.0 per cent and 67.8 per cent protein (N × 6.25), respectively. These figures were used in computing the composition of the regeneration diet which furnished 81.8 per cent of the total dietary protein as lactalbumin. The error in these experiments results from ignoring the probable composition of the non-protein nitrogen fraction of the lactalbumin. This fraction amounted to approximately 20 per cent of the total nitrogen and was undoubtedly composed, in large part at least, of hydrolysate of protein. Assays by Mueller, Kemmerer, Cox and Barnes (18) of casein and casein

hydrolysate suggest that lactalbumin hydrolysate may be the dietary equivalent of the intact protein. The twelve experiments in this series yielded the following assay values: 0.55, 0.62, 0.63, 0.69, 0.76, 0.77, 0.78, 0.84, 0.90, 0.90, 0.95, 1.12. The potency value or average of the assay values was 0.793. The data suggested that lactalbumin was an unusually effective protein for serum albumin synthesis and rendered it obligatory to exclude by further experimentation the possibility that the high value was the result of the error mentioned above.

In the second series of assays a new type of lactalbumin was utilized. The results of the first series had encouraged us to attempt to incorporate some of the original lactalbumin in the diets of several nephrotic children. It was quickly learned that the product was not suitable. It was insoluble in water, milk or other fluids and when mixed with such liquids it remained as a gritty setliment which the children could not be persuaded to imbibe. The difficulty was brought to the attention of Dr. G. C. Supplee of the Borden Milk Company. It was then learned that the original product had been separated from milk whey by heat coagulation before being dried and ground. Being in the denatured form the protein could not be returned to its original soluble state. By appropriate adjustment of pH and the ionizable mineral content, Dr. Supplee was able to prepare a soluble form of lactalbumin. This new form was used in the second series of assays. Analysis revealed a protein content ($N \times 6.25$) of 78.6 per cent. Non-protein nitrogen was not determined and it was assumed that all of the nitrogen was in a form which made it the dietary equivalent of protein. When incorporated in the regeneration ration, 81.8 per cent of the total dietary protein was furnished by the lactalbumin. The results of twelve experiments with the soluble form of lactalbumin are presented in Table V. The assay values vary from 0.48 to 1.10 and yield an average or potency value of 0.773. Although the result is slightly lower than that obtained in the first series of assays, the difference is not so great as might have been expected. It is possible that the soluble lactalbumin was more completely absorbed during digestion than the insoluble form, a circumstance which would tend to compensate for the different quantities incorporated in the diet.

One additional experiment was performed with the soluble lactalbumin. In the course of another study dog 6–95 had been maintained on the basal low-protein diet for a period of 22 weeks. The serum albumin concentration, originally 3.88 grams per cent, had declined to 1.31 grams per cent. Marked ascites had developed. Nevertheless, the appetite and general vitality were still surprisingly good. This animal was placed on the standard regeneration diet with the added protein in the form of lactalbumin. In order that the experiment should parallel the conditions of the previous assay tests, the

TABLE V

Assays of Soluble Lactalbumin for Albumin Formation

DOG	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
	Initial	Depletion	Regeneration	Loss	Gain	
	grams	grams	grams	grams	grams	
9-30	4.18	3.06	4.01	1.12	0.95	1.10
3-93	3.94	2.85	3.78	1.09	0.93	1.08
3-34	3.93	2.65	3.41	1.28	0.76	0.91
3-35	3.81	2.56	3.31	1.25	0.75	0.90
6-93	4.24	3.39	4.11	0.85	0.72	0.87
6-96	4.24	3.47	4.18	0.77	0.71	0.86
9-29	4.15	2.74	3.38	1.41	0.64	0.79
9-40	4.32	3.72	4.18	0.60	0.46	0.61
6-94	3.73	3.11	3.55	0.62	0.44	0.59
6-48	3.92	2.93	3.33	0.99	0.40	0.55
5-31	3.91	2.55	2.94	1.36	0.39	0.54
9-31	4.00	2.44	2.77	1.56	0.33	0.48

Potency value: 0.773 ±0.042 (P.E.).

body weight of the dog after the first 3 weeks on the basal ration was used in computing the total amount of regeneration diet to be fed. The course of regeneration of the serum albumin, depicted in figure 1, was followed by analyses made at two-day intervals. Diuresis set in on the third day and continued during the next 5 days to complete elimination of the ascites. The albumin concentration rose progressively until on the 26th day it reached 4.06 grams per cent. Thereafter only minor fluctuations occurred. The course of replenishment was along the linear path described in earlier experiments (9) of shorter duration. To determine the rate of regeneration a straight

line was fitted by the method of least squares to the results of the fourteen analyses for serum albumin. The slope of this line indicated a regeneration rate of 0.098 gram per cent per day. The rate can be compared with the previous assay values by calculating the regeneration increment over a seven-day period and adding the usual 0.15 as an allowance for maintenance. The result, 0.835, is

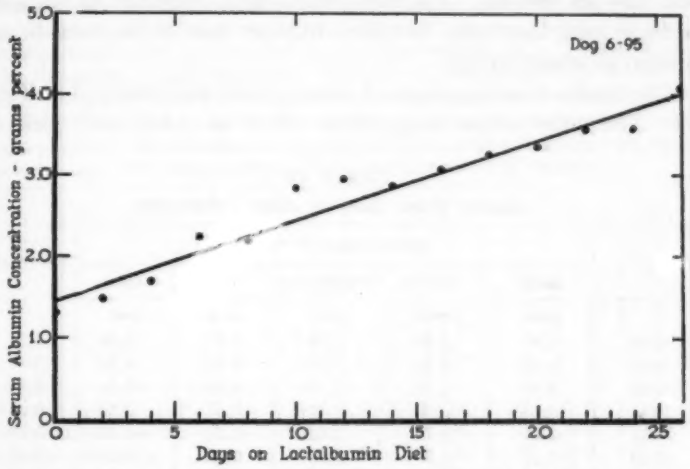


FIG. 1. Progressive rise in serum albumin concentration during maintenance on the standard regeneration diet with added protein in the form of lactalbumin. The dog had been receiving the basal low protein ration for 22 weeks, the albumin concentration had fallen from an original level of 3.88 grams per cent to 1.31 grams per cent, before the regeneration phase was begun. The black dots refer to the results of analyses. The straight line was fitted to the results by the method of least squares.

in good agreement with the findings in the regular assay tests. The experiment is the first in which it has been demonstrated that the velocity of regeneration on a standard dietary intake can be maintained from an extremely low level of albumin concentration until a normal level has been reached.

Wheat Gluten. The assays of wheat gluten were undertaken because of the important role of wheat in the American dietary and not with the expectation that any cereal protein would prove to be par-

ticularly potent. The only wheat product containing enough protein for the practical preparation of the regeneration diet appeared to be the wheat gluten used chiefly in the manufacture of low-carbohydrate flour for diabetics. The wheat gluten utilized in the assay tests was found to have a protein content (N × 6.25) of 79.1 per cent and was stated by the manufacturer to contain 2.5 per cent carbohydrate and 1.06 per cent fat. The regeneration diet, computed on the basis of these analytical data, furnished 81.9 per cent of the total dietary protein as wheat protein.

The results of seven assays of wheat gluten are presented in Table VI. The assay values range from −0.18 to +0.53 and yield an

TABLE VI

Assays of Wheat Gluten for Albumin Formation

DOG	SERUM ALBUMIN PER 100 CC.					ASSAY VALUE
	Initial	Depletion	Regeneration	Loss	Gain	
	grams	*grams*	*grams*	*grams*	*grams*	
6-93	4.45	3.38	3.76	1.07	0.38	0.53
6-96	4.47	3.56	3.80	0.91	0.24	0.39
3-35	3.81	2.58	2.79	1.23	0.21	0.36
3-93	3.64	2.67	2.82	0.97	0.15	0.30
9-31	4.29	2.76	2.64	1.53	−0.12	0.03
9-30	3.72	3.37	3.24	0.35	−0.13	0.02
5-31	3.93	3.19	2.86	0.74	−0.33	−0.18

Potency value: 0.207 ±0.065 (P.E.).

average or potency value of 0.207. The number of assays is too small to establish an accurate potency value. They are sufficient, however, to indicate that the protein of wheat gluten is relatively ineffective as a stimulator of serum albumin synthesis.

DISCUSSION

Because of the variability among replicate assays of any one food protein, the accuracy with which a potency value has been determined in this work depends not only on the number of assays but also on the degree of consistency or variability exhibited throughout each series of tests. This element of reliability must be considered before it is possible to conclude that one type of protein is more or

less effective than another. Calculations have therefore been made of the significance of the difference between two potency values for all possible comparisons among the food proteins dealt with in this and in previous reports. These data are collected in Table VII.

TABLE VII

Statistical Evaluation of the Significance of the Potency Values for Serum Albumin Synthesis

The food proteins are arranged in the left-hand column in descending order of effectiveness. Results are shown for all possible comparisons in the series. Values of the probability integral below the 1 per cent level of significance are indicated by the letter H, that is, the differences are highly significant. Values of the integral above the 10 per cent level are shown by the letter I, that is, the differences are insignificant. Values between 1 per cent and 10 per cent are indicated by numerals which refer to the upper boundary of each step interval. For example, the numeral 5 indicates a level of significance of between 4 and 5 per cent. The interpretation of these values is explained in the text.

	GELATIN	WHEAT GLUTEN	CASEIN	BEEF LIVER	BEEF CHUCK	COW'S MILK	EGG (WHOLE)	EGG (ALL ASSAYS)	COW'S COLOSTRUM	EGG WHITE	BEEF SERUM (DRIED)	BEEF SERUM (ALL ASSAYS)	SOLUBLE LACTALBUMIN
Beef serum (fresh)	H	H	H	H	H	H	4	H	9	4	I	I	I
Soluble lactalbumin	H	H	H	H	H	H	4	H	9	4	I	I	—
Beef serum (all assays)	H	H	H	H	H	H	3	H	6	3	I	—	
Beef serum (dried)	H	H	H	H	H	H	5	2	10	4	—		
Egg white	H	H	H	H	H	H	I	I	I	—			
Cow's colostrum	H	H	H	3	5	7	I	I	—				
Egg (all assays)	H	H	H	H	H	2	I	—					
Egg (whole)	H	H	H	2	4	6	—						
Cow's milk	H	H	I	I	I	—							
Beef chuck	H	H	I	I	—								
Beef liver	H	2	I	—									
Casein	H	H	—										
Wheat gluten	6	—											

The comparisons were made by computing Student's t for each pair of potency values according to the method of Fisher (19). Values of the probability integral corresponding to t were taken from the more extensive tables of Treloar (20). Interpretation of the tabulated data will be facilitated by remembering the prevalent custom (19) of accepting levels of 5 per cent or less for the probability integral

as indicative of a significant difference between the items undergoing comparison; values of 1 per cent or less are accepted as evidence of a highly significant difference. In Table VII the actual values of the probability integral are given only in the range from 1 to 10 per cent. Values above 10 per cent are indicated by the letter I, which may be read "insignificant." Values below 1 per cent are indicated by the letter H, to be read "highly significant."

With one exception the values reported in Table VII were computed from data collected by the author and his associates. The exception concerns casein. Recently Mueller, Kemmerer, Cox and Barnes (18) have reported nine assays of casein for efficiency in albumin formation with a resulting potency value of 0.476. This figure does not differ significantly from that of 0.388 previously reported by the author on the basis of twelve assays. The significance of the comparisons between casein and the other food proteins has therefore been enhanced by combining the two series of assays. The resulting potency value for casein of 0.425 is based on 21 assays and has a probable error of ± 0.022.

Pertinent data on all of the food proteins so far tested are given in Table VIII. The foods are listed in descending order of potency and are arranged in four groups. The grouping was made on the basis of the detailed data of Table VII and is intended as an approximate description only of these findings. In general the proteins in any one group differ significantly in effectiveness from those in the other three groups. Within each group the exact order of the foods has not been established with statistical certainty. Thus, casein in the third group is clearly more potent than wheat gluten and gelatin which comprise the fourth group. It is plainly less effective than any of the proteins in the first two groups but it cannot be said to differ from the other proteins of the third group, that is, from milk, beef chuck, or beef liver. The exact rank-order position of cow's colostrum is less certain. Here there were only nine assays among which the variability was relatively large. Colostrum has not been proved to be either less effective than lactalbumin or beef serum in the first group, nor more effective than cow's milk in the third group. Lactalbumin, because of its high rating, deserves special comment. The superiority of this protein over both egg white and whole egg

was established at the 4 per cent level of significance; the combined evidence from the two series of experiments with egg showed a highly significant difference at the 0.95 per cent level. The position of lactalbumin in the first group is therefore certain on the basis of this evidence alone. Additional observations supporting the high rating given to lactalbumin have already been described.

The studies of Whipple and associates in Rochester (1, 2, 3, 4, 5) on diet and the regeneration of serum protein have utilized the technic of plasmapheresis to elucidate differences in the regenerating potency of various food proteins. Briefly, a dog maintained on a basal ration is subjected to daily plasmapheresis until the volume of bleeding required to maintain a steady state of serum protein depletion has become constant. By analysis of the removed plasma the daily rate of plasma protein production can be determined. The food protein undergoing test is then added to the diet for a period of one week. Plasmapheresis is continued at appropriate volumes during this and subsequent weeks until the basal output has again reached its constant value. The plasma protein removed during

TABLE VIII

The Efficiency of Different Food Proteins for Synthesis of Serum Albumin

SOURCE OF FOOD PROTEIN	POTENCY VALUE	NUMBER OF ASSAYS	PROBABLE ERROR
Beef serum (fresh)	0.801	11	0.053
Soluble lactalbumin	0.773	12	0.042
Beef serum (all assays)	0.770	22	0.030
Beef serum (dried)	0.739	11	0.029
Egg white	0.616	11	0.023
Cow's colostrum	0.611	9	0.042
Egg (all assays)	0.608	23	0.020
Egg (whole)	0.602	12	0.033
Cow's milk	0.483	11	0.021
Beef chuck	0.475	12	0.021
Beef liver	0.445	11	0.025
Casein	0.425	21	0.022
Wheat gluten	0.207	7	0.065
Gelatin	−0.093	4	

these weeks in excess of the basal output is taken as a measure of the effectiveness of the food protein. The result can be expressed either as a "potency ratio," which gives the grams of test food required to yield 1 gram of serum protein or in terms of number of grams of serum protein produced by feeding 100 grams of the food protein. Since the published protocols in these experiments usually supply data on the albumin and globulin fractions of the plasma protein, it is possible in most instances to calculate the number of

TABLE IX

Relationship between Estimates of the Potency of Different Foods in Promoting the Synthesis of Serum Protein (a) as Determined by the Plasmapheresis Technic of Whipple and Associates for Total Serum Protein, (b) as Computed from the Data of Whipple for Serum Albumin, (c) as Measured by the Depletion Technic for Serum Albumin

The figures yielded by the plasmapheresis technic refer to grams of serum protein produced by feeding 100 grams of dietary protein. The data are arranged in descending order of the potency values by the depletion technic.

SOURCE OF FOOD PROTEIN	PLASMAPHERESIS TECHNIC		DEPLETION TECHNIC—ALBUMIN
	Total protein	Albumin	
Beef serum (fresh)	38	21	0.801
Lactalbumin	18	7.3	0.773
Beef serum (dried)	28+	16+	0.739
Egg white	17	9.3	0.616
Beef muscle	18	8.1	0.475
Liver	15	7.3	0.445
Casein	10	4.1	0.425
Gelatin	7	3.6	−0.093

grams of *serum albumin* produced by feeding 100 grams of the food protein. In a previous paper (11) in which the potency values of six foods (fresh beef serum, egg white, beef muscle, liver, casein and gelatin) determined in our Columbia laboratory were compared with albumin potency values calculated from the Rochester data, the order of effectiveness was identical in both series. Table IX has been prepared to bring this comparison up to date. It is clear that the parallelism exhibited by seven of the eight food proteins does not hold in the case of lactalbumin. The findings in this laboratory indicate that lactalbumin is not significantly different from beef serum

in promoting serum albumin synthesis. The findings in the Rochester laboratory ascribe to it a much lower potency which is of the same order as that of liver and skeletal muscle.

The methods of assay in use in the two laboratories are entirely different. It appears significant that in most instances one method has supported the findings of the other. Madden and Whipple (12) believe that the plasmapheresis technic measures *total capacity* for formation of serum protein as opposed to the depletion technic in use at Columbia which measures "relative differences in *rate*" of albumin formation. They suspect that the two methods may not always yield proportional results. It is undoubtedly true that the continuous removal of plasma protein by plasmapheresis makes a more specific demand on the test food than is realized when the entire organism has been depleted by deprivation of dietary protein. The depletion technic, however, does more than record relative differences in rate of albumin formation. The potency values which it yields are immediately translatable into figures which express the average rise in albumin concentration produced in a deficiency state which is closely similar to that encountered in man. If the two methods should fail to agree, it would seem that results by the depletion technic should find greater usefulness in the preparation of human diets. The lack of agreement in the case of lactalbumin may, however, have another explanation. The depletion technic, because it is simple, allows the performance of replicate assays on a fairly large number of animals. Even though the biological variability among the assays may be greater than is encountered in the plasmapheresis technic, nevertheless the replicate results furnish measures of the variability which are then available to assess the accuracy of the potency value. On the other hand the plasmapheresis technic is laborious and in most instances it has been necessary to assess the food proteins on the basis of a single assay. When several assays have been run the results have not always agreed closely. This fact has been noted by Madden and Whipple (12). It may well be that lactalbumin, which was assessed on the basis of one experiment (2), would in replicate assays by this method yield a different result. The possibility is suggested by other experiments from the Rochester laboratory (21) in which cystine is rated as a "key amino acid" in

promoting serum protein production and by the known relatively high cystine content of lactalbumin (22).

SUMMARY

A method of assaying various food proteins for efficiency in promoting the formation of serum albumin is reviewed. The results of 75 assay experiments, which lead to the establishment of "potency values" for six food proteins, are reported.

Dried beef serum with a potency value of 0.739 is a superior protein for producing serum albumin synthesis. The value is not significantly different from that of 0.801, previously obtained in assays of fresh beef serum.

Whole egg with a potency value of 0.602 is a good protein for inducing serum albumin synthesis. The value is almost identical with that of 0.616, previously obtained in assays of egg white.

Cow's milk with a potency value of 0.483 is fairly well utilized for the formation of serum albumin. The result is somewhat, not significantly, higher than the value 0.388, previously obtained in assays of casein.

Cow's colostrum with a potency value of 0.611 appears to furnish good protein for forming serum albumin. Only nine assays were made and the result is less reliable than with most of the other foods. The value is about what would be expected if the protein of colostrum were a mixture of the proteins of milk and beef serum.

Lactalbumin with a potency value of 0.773 is a superior protein for inducing the synthesis of serum albumin. There is no evidence that it differs in effectiveness from either fresh or dried beef serum but superiority over egg protein can be demonstrated. Support for the high rating given to lactalbumin was found in an additional experiment in which the feeding of this protein at the standard level brought about in 26 days an increase in albumin concentration in the serum from 1.31 grams per cent to 4.06 grams per cent.

Wheat gluten with a potency value of 0.207 is a poor protein for producing serum albumin formation.

The relative effectiveness of the foregoing six foods and of the six foods previously reported on (fresh beef serum, egg white, beef muscle, beef liver, casein, gelatin) is evaluated by conventional statistical

procedure. The values are also compared with the results of assays by Madden and Whipple in which the power of various food proteins to produce serum protein has been measured in plasmapheresis experiments.

It is a pleasure for the author to express his indebtedness: to Mr. E. F. Pike of the Armour Laboratories in Chicago for preparing the dried beef serum under special conditions so as to insure purity and cleanliness; to Dr. L. T. Wilson of the Walker-Gordon Laboratory Company, Inc., in Plainsboro, New Jersey, for his labor in collecting and shipping the first colostrum milk from cows; to Dr. G. C. Supplee of the Borden Company in Bainbridge, New York, for his cooperation in making available a soluble form of lactalbumin; to Mr. L. D. Johnson of Mead Johnson and Company in Evansville, Indiana, for his kindness in continuing to supply cod liver oil for the kennel rations.

BIBLIOGRAPHY

1. Holman, R. L., Mahoney, E. B., and Whipple, G. H.: *J. Exp. Med.*, **59:** 251, 1934.
2. Pommerenke, W. T., Slavin, H. B., Karlher, D. H., and Whipple, G. H.: *J. Exp. Med.*, **61:** 261, 1935.
3. McNaught, J. B., Scott, V. C., Woods, F. M., and Whipple, G. H.: *J. Exp. Med.*, **63:** 277, 1936.
4. Madden, S. C., Winslow, P. M., Howland, J. W., and Whipple, G. H.: *J. Exp. Med.*, **65:** 431, 1937.
5. Madden, S. C., George, W. E., Waraich, G. S., and Whipple, G. H.: *J. Exp. Med.*, **67:** 675, 1938.
6. Melnick, D., Cowgill, G. R., and Burack, E.: *J. Exp. Med.*, **64:** 877, 1936.
7. Melnick, D., Cowgill, G. R., and Burack, E.: *J. Exp. Med.*, **64:** 897, 1936.
8. Melnick, D., and Cowgill, G. R.: *J. Nutrition*, **13:** 401, 1937.
9. Weech, A. A., and Goettsch, E.: *Bull. Johns Hopkins Hosp.*, **63:** 154, 1938.
10. Weech, A. A., and Goettsch, E.: *Bull. Johns Hopkins Hosp.*, **63:** 181, 1938.
11. Weech, A. A., and Goettsch, E.: *Bull. Johns Hopkins Hosp.*, **64:** 425, 1939.
12. Madden, S. C., and Whipple, G. H.: *Physiol. Rev.*, **20:** 194, 1940.
13. Weech, A. A., Goettsch, E., and Reeves, E. B.: *J. Exp. Med.*, **61:** 299, 1935.
14. Atwater, W. O., and Bryant, A. P.: *U. S. Dept. Agric., Office Exp. Stations, Bull., 28:* 1906.
15. Rogers, L. A.: *Fundamentals of dairy science*, 2nd ed., (Reinhold Publishing Corporation, New York), 1935.
16. Crowther, C., and Raistrick, H.: *Biochem. J.*, **10:** 434, 1916.
17. Wells, H. G., and Osborne, T. B.: *J. Infect. Dis.*, **29:** 200, 1921.
18. Mueller, A. J., Kemmerer, K. S., Cox, W. M., and Barnes, S. T.: *J. Biol. Chem.*, **134:** 573, 1940.

19. FISHER, R. A.: *Statistical methods for research workers*, 5th ed., (Oliver and Boyd, Edinburgh), 1934.
20. TRELOAR, A. E.: *An outline of biometric analysis*, 2nd ed., (Burgess Publishing Co., Minneapolis), 1936.
21. MADDEN, S. C., NOEHREN, W. A., WARAICH, G. S., AND WHIPPLE, G. H.: *J. Exp. Med.*, **69**: 721, 1939.
22. BEACH, E. F., BERNSTEIN, S. S., HOFFMAN, O. D., TEAGUE, D. M., AND MACY, I. G.: *J. Biol. Chem.*, **139**: 57, 1941.

NUTRITIONAL DERMATOSES IN THE RAT

VII. Notes on the Posture, Gait and Hypertonicity Resulting from a Diet Containing Unheated, Dried Egg White as the Source of Protein[1]

MAURICE SULLIVAN, M.D., LAWRENCE KOLB, M.D., AND JANE NICHOLLS, M.Sc.

From the Departments of Dermatology and Neurology, School of Medicine, and the Department of Biochemistry, School of Hygiene, The Johns Hopkins University

Submitted for publication January 13, 1942

When young rats are fed a diet containing uncooked egg white as the source of protein, there develops a disease characterized by poor growth, generalized pruritic, exfoliative dermatitis, abnormal posture, abnormal gait and hypertonicity. The cutaneous signs have been carefully described (1). The posture, gait and hypertonicity have not received sufficient attention. The present experiment was undertaken to ascertain whether the posture, gait and hypertonicity were caused by an anatomical defect in the central nervous system.

Rats weighing 30 to 35 grams and of approximately 18 days of age were fed the following diet: Dried commercial egg white, 30 per cent, cornstarch, 17.7 per cent, sucrose, 18.5 per cent, McCollum Salts, No. 51, 5.8 per cent, peanut oil, 15 per cent, cod liver oil, 3 per cent, and a yeast extract equivalent to 10 per cent dry yeast. Within 4 to 8 weeks there was generalized, pruritic, exfoliative dermatitis. At the height of the cutaneous involvement, when pruritus was exquisite, the abnormal posture and gait and the hypertonicity were remarked. The striking feature of the posture was the excessive elevation and rounding of the lumbo-sacral portion of the spine (Fig. 1). The arching or bowing of the spine was more pronounced than that observed in the usual humped positions associated with various deficiency diseases of the rat (2). Roentgenograms of a severely affected living rat showed, in addition to the caudal hump, an acute dorsal

[1] Aided by a grant from the Rockefeller Foundation Fluid Research Fund.

curvature in the lower cervical and upper thoracic spine with an abrupt curvature in the lower portion of the thoracic spine (Fig. 2). This raised the arch of the back high above the head. At rest the posterior extremities were usually in greater extension at all of the joints than in the healthy rat. The forelegs were extended and the head was thrust downward and forward. When the rat walked or ran, it elevated the hind legs excessively and often stepped off of the tips of the digits rather than the whole tarsus (Fig. 1). There was hyperextension of the posterior extremities, which exaggerated the elevation of the caudal hump and shifted some of the weight forward onto the shorter, over-extended forelegs. The gait was deliberate. When the rat attempted to move rapidly, it often hopped. There was no ataxia. Noise or handling frequently caused tremors. Hypertonicity was a prominent symptom. It occurred after the dermatitis was extensive and pruritus was exquisite and may have been due in large part, if not entirely, to irritability provoked by pruritus. The signs persisted with maximum severity until biotin or biotin-rich foods were administered, or until the raw egg white was replaced either by cooked egg white or by another protein. After 3 or 4 days of treatment with biotin, the animal was relaxed and assumed a normal posture and gait.

Microscopic examination of the skin showed the signs previously described (1. j) as characteristic of the disease, namely, extensive hyperkeratosis and some parakeratosis, broken hair shafts, serous exudate and much sudanophilic material intermingled with the hyperkeratotic lamellae, acanthosis and edema in the early stages, wide dilatation of the follicular orifices and atrophy of the epidermis in the late stage. Except for slight atrophy there were no abnormal findings in the internal organs. The central nervous system and a portion of the sciatic nerve were removed after perfusing the body through the heart with a 10 per cent formalin-saline solution immediately after death. Sections were made either by using the frozen section technic, or by embedding the tissues in paraffin. The following staining methods were used: Herxheimer, Marchi, various modifications of the Weigert technic, thionin, hematoxylin eosin and Bielschlowsky. The fore brain, hind brain, spinal cord, posterior root ganglion and sciatic nerve were studied by these various methods.

Nothing abnormal was found. These findings differed from those of Findlay and Stern, (1. h), who reported diffuse infiltration of round cells in the grey and white matter of the spinal cord, early vacuolar changes in a few cells of the anterior horn, Marchi droplets particularly near the nodes of Ranvier of the sciatic nerves. Cellular infiltration was not observed in rats in the present experiment, nor was vacuolization of the ganglion cells seen when good fixation was obtained by immediate perfusion of the body with fixing fluid. However, in some of our early experiments, when the animals were not perfused immediately after death, vacuolization of the ganglion cells of the spinal cord and of the brain were observed. In order to determine whether the vacuolization was due to post mortem changes, a group of normal animals was killed and instead of being perfused and immediately fixed, the brains and cords were removed and placed in fixing solution after periods of from 15 minutes to 6 hours; in these there were all stages of vacuolization including complete cellular disintegration. The importance of immediate fixation by perfusion in studies of the nervous system should be emphasized.

Histologic examinations of the muscles of the posterior extremities were made of 16 of the severely affected rats varying in age from 11 to 31 weeks. In the sections of the animals from 16 to 31 weeks, swelling and increase in the number of the sarcolemmal cells were observed (Fig. 3). In some cases this was so extensive that whole muscle fibres appeared to be destroyed. The earliest detectable change was a loss of the longitudinal striations. There was a great variation in the diameter of the muscle fibers and the average diameter was slightly below that of muscles of stock rats. As there were no cellular changes in the central nervous system, the muscle lesion was not considered to have been secondary to changes in motor ganglion cells and, therefore had to be explained on a basis other than a neurologic lesion due to an anatomical defect. In some respects the microscopic changes in the muscles of the rats in this experiment corresponded to those reported by Findlay and Stern, who found that the muscle fibres were thinner than average, that the sarcolemmal nuclei were more prominent and numerous than usual and that the intramuscular connective tissue and nerve fibres showed an increase in cellular elements.

Increase in sarcolemmal nuclei has been reported in vitamin E deficiency (3). Inasmuch as the experimental rations employed by Findlay and Stern and by us were low in vitamin E, the question of complicating vitamin E deficiency arose. There were no gross signs suggestive of vitamin E deficiency during the experiment. Such signs appear after 16 or more weeks' depletion of vitamin E and differ considerably from the signs described above. The hypertonic state of the rat in this experiment contrasts with the flaccid state of the rat depleted of vitamin E, in which there is a weakness, particularly of the abductors of the thighs, so that the legs are spread wide apart.

The weakness extends upwards and the animal is eventually unable to move the lower portions of its body. It seems to have lost sensation as it may lie or step upon its tail. In order to observe the effect of the administration of vitamin E upon the posture, gait and hypertonicity, a group of 6 rats was fed the egg white diet supplemented with alpha tocopherol in doses of 20 mg. orally and 20 mg. subcutaneously 2 times a week. The signs of egg white injury were not delayed or modified. Microscopic examination of the muscles of the 6 rats to which the alpha tocopherol was administered showed a variation in the diameter of muscle fibres which approximated that of stock rats. This phase of the experiment was terminated at 14 weeks and at that time there was no increase in sarcolemmal nuclei. Although it was clearly demonstrated that the addition of alpha tocopherol had no influence on the gross signs and symptoms of the disease, the period of 14 weeks was too short to permit the conclusion that the muscle lesion was prevented by alpha tocopherol. Further experiments are being conducted in collaboration with Dr. C. G. MacKenzie in order to investigate the possibility that the muscle lesion was due to complicating vitamin E deficiency. The question of the etiology of the muscle lesion wants elucidation, particularly in view of the opinion expressed by Eddy and Daldorf (4), namely, that similar if not identical lesions are common in apparently unrelated dietary deficiencies. Occasionally we have noted that in the muscles of stock rats there were a few areas where there was an increase in the sarcolemmal nuclei.

An intravenous injection of quinine hydrochloride was given to one rat. This failed to relieve the hypertonicity. Prostigmin administered to another rat had no effect. A single myographic reading from

the muscles of the calf obtained after direct stimulation of the sciatic nerve showed no evidence of repetitive discharge. This indicated that muscle rigidity was not myotonic in origin. Roentgenograms showed no evidence of disease of the bone and after administration of biotin, the spinal curvature promptly disappeared. Therefore, the curvature probably was not due to an abnormality of the bone.

In our early experiments (1. j) a commercial yeast autolysate was used as a source of the vitamin B complex and was fed at a 5 per cent level. Later a yeast extract was prepared by a method which resulted in a product that subsequently proved by rat assay to be low in the vitamin B complex. In both circumstances there was a rapid loss of weight in 7 to 10 weeks, followed by a flaccid paralysis, particularly of the hind extremities, and death. Administration of massive doses of biotin (vitamin H concentrate) failed to prevent paralysis and death. However, when additional thiamin was fed as a supplement, the paralysis was prevented and when a potent yeast extract was substituted for the extract low in vitamin B, rapid growth resulted and the syndrome was produced. György (5) reported that he encountered difficulty in producing the disease and that weight curves showed a slight but continuous tendency to decline when he used certain commercial yeast autolysates as sources of the vitamin B complex in a diet identical with the diet in this experiment. Boas (1. a) stated that some of the rats in her experiments assumed a crouching attitude and displayed a curious swimming movement of the front paws. It is likely that rats fed rations containing large amounts of egg white require an abundance of the vitamin B complex due to persistent diarrhea, poor absorption and utilization (6) and that under the experimental conditions required to produce the disease, there is frequently a superimposed thiamin deficiency.

SUMMARY AND CONCLUSIONS

1. When young rats are fed an experimental ration containing uncooked egg white, there develops a generalized pruritic exfoliative dermatitis. At the height of the cutaneous involvement, abnormal posture, abnormal gait and hypertonicity are usually observed. After several days of treatment with biotin concentrates or foodstuffs containing biotin, the latter signs are rapidly reversed.

2. There are no anatomical changes in the central nervous system.

3. It is suggested that the hypertonicity may be due to irritability provoked by severe pruritus and that the rigidity is not myotonic in origin.

4. Flaccid paralysis occurring in connection with experiments on the production of the disease is the result of a complicating thiamin deficiency.

BIBLIOGRAPHY

1. a. BOAS, M. A.: An Observation on the Value of Egg White as the Sole Source of Nitrogen for Young Growing Rats. *Biochem. J.*, **18:** 422, 1924.
   b. BOAS, M. A.: The Effect of Desiccation upon the Nutritive Properties of Egg White. *Biochem. J.*, **21:** 712, 1927.
   c. FRIEDBERGER, E.: Ueber den Anschlagswert and uber Nahrschaden bei einseitiger Verfutterung von Huhnerei. *Deutsche. med. Wchnschr.*, **52:** 1760, 1926.
   d. SCHEUNERT, A., AND WAGNER, E.: Ueber den Einfluss des Kochens auf den Nahrwert des Huhnereies. *Deutsche. med. Wchnschr.*, **53:** 1258, (July 22) 1927.
   e. STENQVIST, F.: Roh und gekochte Huhnereier als einsiger Nahrungsmittel fur Wachsende Ratten. *Deutsche. med. Wchnschr.*, **54:** 1920, (Nov.) 1928.
   f. GYORGY, P.: *Stoffwechsel und Immunobiologie der Haut. Handbuch. d. Kinderheilkunde*, p. 45, (F. C. W. Vogel, Berlin), 1935.
   g. PARSONS, H. T.: The Physiological Effects of Diets Rich in Egg White. *J. Biol. Chem.*, **90:** 351, (Jan.) 1931.
   h. FINDLAY, G. M., AND STERN, R. O.: Syndrome in Rat Resembling Pink Disease in Man. *Arch. Dis. Childhood.*, **4:** 1, (Feb.) 1929.
   i. SALMON, W. D., AND GOODMAN, J. G.: Studies of the Raw Egg White Syndrome in Rats. *J. Nutrition*, **8:** 1, (July) 1934.
   j. SULLIVAN, M., AND NICHOLLS, J.: Nutritional Dermatoses in Rats. V. Signs and Symptoms Resulting from a Diet Containing Unheated, Dried Egg White as the Source of Protein. *Arch. Dermat. and Syph.* (In press.)
2. a. QUINN, E. J., KING, C. G., AND DIMIT, B. H.: A Study of the Effects of Certain Diets upon the Growth and Form of Albino Rats. *J. Nutrition*, **1:** 7, (Sept.) 1929.
   b. ARON, H.: Untersuchungen uber die Beeinflüssung des Wachstums durch die Ernährung. *Berliner Klin. Wochenschr.*, **51** Part 1: 972, (May) 1914.
   c. JACKSON, C. M.: Changes in the Relative Weights of the Various Parts, Systems and Organs of Young Albino Rats Held at Constant Body Weight by Underfeeding for Various Periods. *J. Exper. Zool.*, **19:** 99, (August) 1915.
   d. WOLBACH, S. B., AND HOWE, P. R.: Tissue Changes after Vitamin A Deficiency. *J. Exper. Med.*, **42:** 753, (Dec.) 1925.

e. OLESON, J. J., BIRD, H. R., ELVEHJEM, C. H., AND HART, E. B.: Additional Nutritional Factors Required by the Rat. *J. Biol. Chem.*, **127:** 23, (Jan.) 1939.

f. SULLIVAN, M., AND NICHOLLS, J.: The Nutritional Approach to Experimental Dermatology. Nutritional Dermatoses in the Rat. II. Skin Changes in Rats Deficient in the Entire Vitamin B Complex Other than Thiamin. *J. Invest. Derm.*, **3:** 337, (Aug.) 1940.

g. SULLIVAN, M., AND NICHOLLS, J.: Nutritional Dermatoses in the Rat. IV. Riboflavin Deficiency. *J. Invest. Derm.*, **4:** 181, (June) 1941.

3. a. RINGSTED, A.: A Preliminary Note on the Appearance of Paresis in Adult Rats Suffering from Chronic Avitaminosis E. *Biochem. J.*, **29:** Part I: 788, (March) 1935.

b. BLUMBERG, H.: A Growth Deficiency Disease, Curable by Wheat Germ Oil. *J. Biol. Chem.*, **108:** 227, (Jan.) 1935.

c. BURR, G. O., BROWN, W. R., AND MOSLEY, R. L.: Paralysis in Old Age in Rats on a Diet Deficient in Vitamin E. *Proc. Soc. Exper. Biol. Med.*, **36:** 780, (June) 1937.

d. EINARSON, L., AND RINGSTED, A.: *Effect of Chronic Vitamin E Deficiency on The Nervous System and the Skeletal Musculature.* Levin and Munksgaard. p. 133, (Ejnar Munksgaard, Copenhagen), 1938.

4. EDDY, W. H., AND DALLDORF, G.: *The Avitaminoses*, p. 419, (The Williams and Wilkins Co., Baltimore), 1941.

5. GYORGY, P.: The Curative Factor (Vitamin H) for Egg White Injury with Particular Reference to its Presence in Different Foodstuffs and in Yeast. *J. Biol. Chem.*, **131:** 733, (Dec.) 1939.

6. a. BATEMAN, W. G.: The Digestibility and Utilization of Egg Protein. *J. Biol. Chem.*, **26:** 263, 1916.

b. BOND, M.: A Modification of Basal Diet for Rat Feeding Experiments. *Biochem. J.*, **16:** 479, 1922.

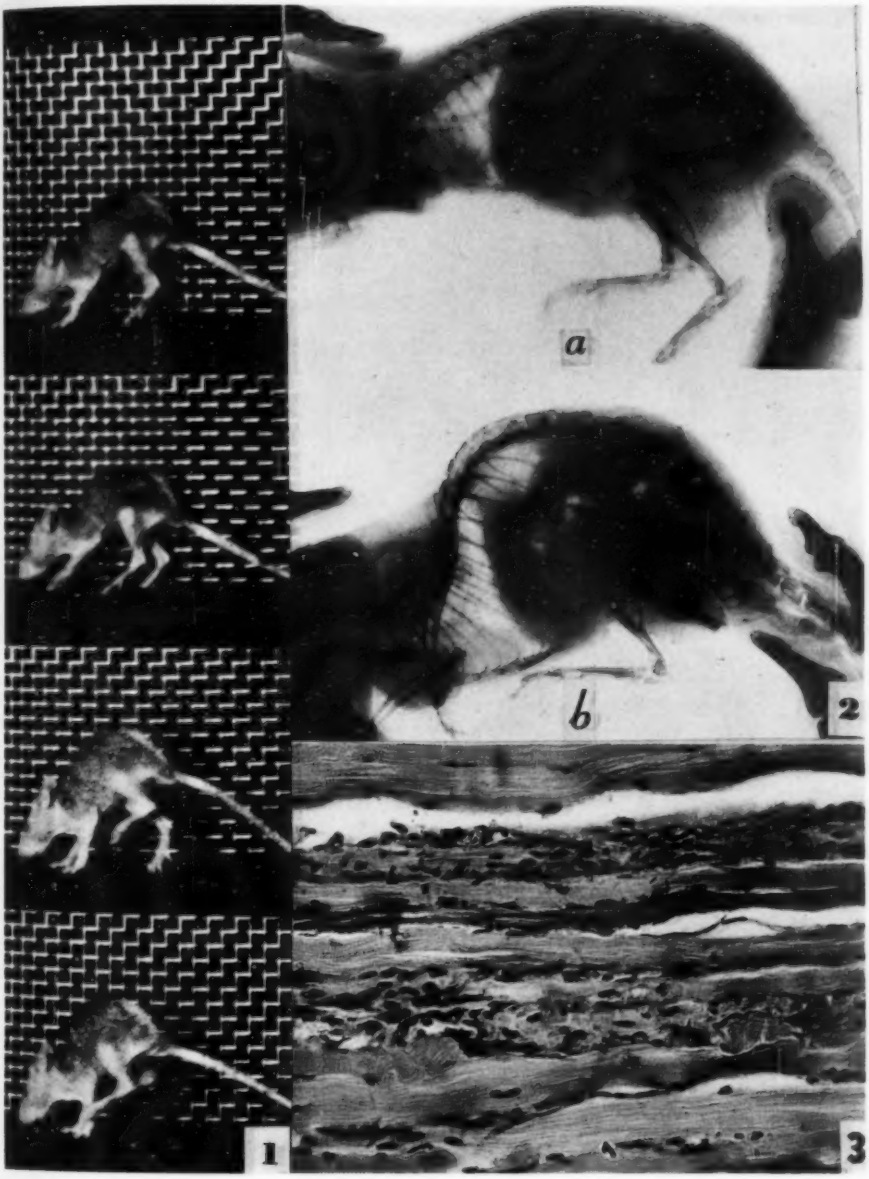
PLATE 1

FIG. 1. Showing the humped posture, the deliberate gait and hypertonicity.

FIG. 2. a. Roentgenogram of normal rat.

b. Roentgenogram of a severely affected rat showing the caudal hump and the acute curvature in the lower cervical and upper thoracic spine with the abrupt curvature in the lower portion of the thoracic spine.

FIG. 3. Microscopic appearance of muscle from the thigh showing increase in the sarcolemmal nuclei (× 250).


a
b
2
1
3

PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

HELD IN THE HURD MEMORIAL HALL, DECEMBER 8TH, 1941
The President of the Society, Dr. Frank B. Walsh, presided.
Abstracts of the papers and discussions follow:

Diabetes in Pregnancy: Case Reports. By L. M. HELLMAN.

Three cases of pregnancy, complicated by maternal diabetes, were presented. These demonstrated three problems, namely:

1. The question of interruption of pregnancy in a severe diabetic with a poor family history.

2. The case of a mild diabetic mother was presented; although she was well regulated, she produced two excessively large children, the first of which was stillborn, and the second was delivered by Caesarean section, being too large to pass safely through the birth canal.

3. The third case was used to illustrate the difficulty of control of diabetes in the pregnant woman. This girl was controlled with difficulty until the 8th month, at which time she went into labor and delivered a stillborn, premature infant. She was in acidosis during labor, and profound coma immediately thereafter.

The question of the recent increase in the number of diabetics seen in the obstetrical department of the Johns Hopkins Hospital was discussed, and it was suggested that this increase was directly related to the widespread use of insulin therapy. The infant stillbirth and neonatal death rate of 27 per cent for diabetics was also pointed out. This high figure, which is nine times the usual clinic rate, was thought to be due in part to the lack of intensive care of diabetic mothers.

DISCUSSION

Dr. Nicholas J. Eastman said that Dr. Hellman had presented these cases in order to emphasize the problems which are encountered in the obstetrical care of diabetic women. In the first case, heredity entered into the decision to sterilize the patient. In the second case, difficulties arose because of the large size of the babies. The problem of the huge babies of diabetic mothers has not yet been solved. It was once thought that careful dietary regulation during pregnancy was the solution; this seems not to be the case. Some of the well-controlled diabetic mothers here have had ten-pound babies three weeks before term. Endocrine factors may be of some importance, as suggested by the work of Priscilla White in Boston. Doctors Delfs and Seegar are now trying to confirm this work here.

In the third case, there was difficulty in regulating the diabetes. The question

may be raised as to whether we are treating these diabetic women as well as we might be. We have a special clinic for treating our cardiac patients during pregnancy. This is under the direction of Dr. Tilghman of the Department of Medicine, and the clinic has been profitable for all concerned. There might be a similar arrangement for our diabetic patients, with cooperation between the departments of Obstetrics and Medicine. Such an arrangement would be extremely satisfactory, and would certainly reduce the mortality of diabetic mothers and babies. The importance of diabetes in obstetrical practice is steadily increasing. Formerly, the maternal mortality was very high, and the vast majority of the infants died. But now most of the mothers live, and may return with second pregnancies; the girl babies live, and under insulin treatment, grow old enough to have children.

Dr. George W. Thorn agreed with Dr. Eastman that a cooperative clinic for the treatment of these patients was desirable. He noted several reasons why the diabetic mother is a difficult diabetic patient. (1) The nausea and vomiting early in pregnancy interfere with the dietary regulation. (2) During pregnancy the renal threshold for sugar is low and it is better to disregard the glycosuria and base the regultion upon acetonuria, while keeping the dietary carbohydrate high. (3) The mother's caloric intake must be held down in order to prevent excessive weight in the child. (4) The mother needs more than the normal caloric intake during pregnancy.

Regulation of the diabetes is most difficult immediately before labor. If too much insulin is given, there is danger of shock; if too little, there is danger of acidosis.

Dr. Edwards A. Park asked whether the enlargement of the baby was a symmetrical one, or merely an increase in the amount of soft tissue.

Dr. Eastman said the enlargement was symmetrical, and involved bone, *etc.* as well as fat, and that some growth factor must be involved as well as the dietary factor.

A Summary of the Clinical Experience with Addison's Disease Treated with Desoxycorticosterone Acetate. By GEORGE W. THORN, SAMUEL S. DORRANCE and WARFIELD M. FIROR.

During the past three years, 54 patients with Addison's Disease have been treated with desoxycorticosterone acetate in the Johns Hopkins Hospital. Of this number 50 have received pellet implantations. The duration of therapy for the 50 patients who have received pellet implantations now exceeds two years. During this period, 7 patients have died. At the present time the condition of the 43 remaining patients may be classified as follows:

Very good	7
Good	20
Fair	12
Poor	4

Of the group of 50, 27 were males. Of the 23 male patients who now survive, 14 or approximately 60% are regularly employed.

Pellets of desoxycorticosterone acetate should be implanted only after the daily maintenance dose of Percorten (synthetic hormone in oil) has been established. This assay is usually conducted with three grams of sodium chloride daily as medication and a daily dose of hormone in oil which will maintain weight and blood pressure without producing edema, hypertension or circulatory insufficiency. After the patient has been maintained for 4–6 weeks by daily injections of hormone, it is then possible to substitute pellets of synthetic hormone on the basis of one pellet for each 0.5 mg. of hormone required daily. If reasonable care is taken in adjusting the dose of hormone and salt, signs and symptoms of overdosage, i.e., edema, hypertension, cardiac enlargement and muscular pains may be avoided in most instances. In all instances reduction of the dose of hormone and salt is followed by a prompt loss of sodium chloride. Desoxycorticosterone acetate does not correct the disturbance in carbohydrate metabolism which many patients exhibit. For this reason, it is desirable that all patients be maintained on a relatively high carbohydrate intake with frequent intermediate feedings unless supplementary adrenal cortical extract is used. Supplementary adrenal extract therapy is definitely indicated during the course of intercurrent infections when it is difficult for patients to maintain adequate intake of carbohydrate.

The reasonable cost of desoxycorticosterone acetate permits most patients to afford adequate hormone treatment. The use of pellet implantation obviates the necessity for daily injections of hormone and results in a considerable increase in efficiency of hormone utilization.

DISCUSSION

Dr. James Bordley said that one would expect a certain mortality in these patients from related diseases, such as tuberculosis. He asked what proportion of the mortality in the present series was due to adrenal insufficiency and what proportion to other disease factors.

Dr. Walter L. Winkenwerder asked whether there were individual variations in the dose requirements for regulation, and whether the duration of the disease prior to treatment bore any relation to the mortality.

Dr. W. Halsey Barker asked whether there was any indication of over-secretion of the adrenal cortex in cases of familial periodic paralysis.

Dr. Thorn said in reply to the questions: (1) that only two of the seven deaths could be attributed directly to adrenal insufficiency. The other five patients died of tuberculosis and intercurrent infections of which streptococcal infections were the most important. With regard to the severe streptococcal infections, it is advantageous to use sulfadiazine which is less likely to cause nausea and vomiting. If active tuberculosis is present, the prognosis is not good. However, in one case the active tuberculous infection was confined to a single kidney, and when this kidney was removed, the patient made a very satisfactory recovery.

(2) That it is rare for a patient to require over five mg. per day of desoxycorticosterone. Larger doses are sometimes necessary during a crisis or during infections. Most patients may be regulated on two to three mg. per day. Over-

dosage of desoxycorticosterone is most commonly associated with two types of unfavorable reactions. The first is characterized by edema, hypertension and cardiac enlargement. The second is characterized by disturbances in muscular and neuromuscular function. This is most likely due to the disturbances in sodium and potassium ratio, i.e., high sodium, low potassium.

(3) That although the paralysis mentioned is much like familial periodic paralysis, there is no evidence of oversecretion of desoxycorticosterone in the latter disease. Both conditions are due to chemical disturbances, but in the case of familial periodic paralysis these chemical disturbances are produced by agents other than desoxycorticosterone.

The Rôle of Isoimmunization in the Pathogenesis of Erythroblastosis Fetalis. By PHILIP LEVINE, Newark, New Jersey.

Evidence was presented that the essential feature in the pathogenesis of erythroblastosis fetalis is isoimmunization of the mother by blood factors in fetal blood inherited from the father. In 90 per cent of the cases the Rh (Rhesus) factor in the fetal blood is responsible for the immunization of the mother. In a random population, male or female, the Rh factor is present in 85 per cent and absent in 15 per cent; but in a series of 153 mothers of erythroblastotic infants more than 90 per cent are Rh negative while the affected infants and husbands of the Rh negative mothers are 100 per cent Rh positive. Furthermore, anti-Rh agglutinins could be demonstrated in about 50 per cent of the Rh negative mothers if the tests were carried out shortly after the delivery of an erythroblastotic infant.

Accordingly, the continual action of the mother's anti-Rh agglutinin on the susceptible fetal blood is the cause of the intra-uterine hemolytic process which characterizes the clinical features of erythroblastosis fetalis. In the remaining cases, i.e., Rh positive mothers, blood factors other than Rh may induce the isoimmunization. At least one such factor could be demonstrated with the aid of atypical agglutinins in the blood of an Rh positive mother of an erythroblastotic infant. This agglutinin acted by preference on Rh negative bloods.

The isoimmunization theory offers a suitable explanation also for the familial nature of erythroblastosis fetalis. The striking familial incidences in certain mothers and the sporadic incidence in others apparently depend upon the homozygosity or heterozygosity of the father's blood.

It is known that mothers of erythroblastotic infants have a high incidence of abortion, miscarriages, and stillbirths. The data on isoimmunization by pregnancy indicate that this same mechanism, that is, action of maternal immune agglutinins, may bring about early death of the fetus. The isoimmunization theory requires that fetal blood, in one form or another, enter the maternal circulation in sufficient quantity to induce immunization. This view is supported by results of experiments which indicate that the Rh factor is probably limited to red blood cells and is not present in body fluids.

Women immunized by pregnancy are subject to intra-group transfusion accidents. Since the Rh factor is responsible for 90 per cent of all instances of iso-

immunization of the mother, these transfusion accidents may be prevented by selecting Rh negative donors for these mothers. An additional precautionary measure is the incubation (one-half to one hour) at 37°C of the mixture of the patient's serum and the donor's cells, followed by slow centrifugation and suspension. This modified compatibility test should be performed even if an Rh negative donor is selected for an Rh negative patient because various human anti-Rh bloods differ somewhat in their specificities.[1]

DISCUSSION

Dr. Hugh Josephs raised the question of what is meant by erythroblastosis neonatorum. First, there is a pathological condition which is non-specific. It may occur in syphilitic babies and it has been reported in sickle cell anemia, congenital hemolytic jaundice and malaria. Secondly, there is the characteristic family history in these patients of the type discussed by Dr. Levine. One wonders how Dr. Levine would account for such peculiarities as (1) the occurrence of erythroblastosis neonatorum chiefly in full term infants while it is rarely reported in premature babies; (2) the rarity of evidences of toxemia during the pregnancies. Although Dr. Levine has described an important factor in erythroblastosis neonatorum, the question remains whether the influence of this factor will explain all of the cases.

Dr. Maxwell N. Wintrobe said that he was troubled by having to postulate that the red blood cells of the fetus or some substance resulting from their breakdown must get into the mother's circulation. Obstetricians ordinarily won't allow that the red blood cells pass through the placenta. Dr. Wintrobe said that he was particularly interested in the concept of the Rh factor because of the light which it had thrown upon hitherto unexplained transfusion reactions. He asked whether there are racial differences in the distribution of the Rh factor.

Dr. Edwards A. Park asked why it was that the first baby escaped erythroblastosis.

Dr. Eastman, in answer to Dr. Wintrobe's question, said that it is known that occasionally villus cells escape into the maternal circulation. If the lining of the chorionic villus can escape, it is possible that fetal elements may also escape. Statistically, one would expect that 12 per cent of matings would be between Rh fathers and Rh- mothers. However, the cases of erythroblastosis fetalis are about one in 400. Possibly it is in only some of the cases that circumstances exist which allow the red blood cells to escape into the maternal circulation.

Dr. Mark Ravitch remarked that it is no longer true that post-transfusion reactions are generally due to mistakes in the routine matching and grouping. Since the blood bank in this hospital was started three years ago, there have been only

---

[1] A complete report of these findings is published in the American Journal of Obstetrics and Gynecology, 1941, **42**: 925.

six severe transfusion reactions and one death. In none of these cases was there a mistake in the routine matching and grouping.

Dr. Levine gave the following answers to the questions which had been asked:

(1) Although most cases of erythroblastosis have been reported in full term infants, there is a high incidence of premature births among these mothers. In the premature infants, the diagnosis of erythroblastosis is difficult to make.

(2) Mothers of infants with hydrops have a high incidence of toxemias; mothers of infants with erythroblastosis do not.

(3) The first baby does not always escape. On the other hand, the first two or three may escape. This may be explained by the fact that more antigenic stimulus is needed by some individuals than by others to produce effective antibody. It is possible to explain 90 per cent or more of the cases of erythroblastosis by this theory. Of the exceptions in the present series, two were syphilitic.

(4) There is a very low incidence of Rh- persons in the colored race and they are practically absent among American Indians.

(5) The incidence of erythroblastosis is stated to be 1 in 440 pregnancies. However, hydrops and mild anemias should be included in the figures for this reaction. This would make the total incidence considerably higher.

(6) With the potent grouping sera now available, there are practically no transfusion accidents resulting from incorrect grouping.

Finally, Dr. Levine called attention to the fact that infants with erythroblastosis who require transfusions respond best if they are transfused with Rh- blood.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

From Cretin to Genius. By SERGE VORONOFF. 281 pp. $2.75. *Alliance Book Corporation, New York, 1941.*

This book represents a summing up by the man who has become famous for his experiments with the grafting of animal glands into cretins and seniles. Voronoff, whose "rejuvenation" claims have caught the popular fancy for a time, tries to "explain" life, genius, heredity, and many other things.

The book appears to be a well-meant but befuddled mixture of interesting autobiographic material, sentimentalism, and a peculiar form of pseudomaterialistic mysticism. Violence is done to semantics when terms, such as intelligence, inspiration, soul, matter and mind, are used naïvely with whatever connotations suit the need or the whim of the moment. Anecdotal examples, taken out of their contexts, are offered with a gullibility worthy of old Robert Burton's "Anatomy of Melancholy". Life is treated sometimes as something like an élan vital, at other times in terms of grossest epiphenomenalism.

Voronoff is, of course, firmly convinced that gland transplantation can make cretins intelligent and seniles vigorous. He is also convinced that thought transference and mind reading are incontestable facts.

A few tidbits of the leading pronouncements are as follows:

"Cerebral matter. . . emits radiations that propel the invisible grains of thinking matter."

"An idea floats in space, ready to fertilize any receptive genius." This serves to explain how an idea expressed by an ancient philosopher can wait around until, centuries later, it slides into the brain of a new genius.

"The quality of genius is located in certain regions of the brain which develop out of all proportion."

"The conscious ego occupies the superficial layers of the brain, the subconscious the lower layers."

The style of writing is fluent, very readable, but sometimes a little too mushy for ordinary tastes. The printers have done an excellent job.

L. K.

Surgical Practice of the Lahey Clinic. 897 pp. Illus. $10.00 *W. B. Saunders Company, Philadelphia and London, 141.*

Surgeons and students of surgery everywhere will welcome this fully illustrated exposition of surgical technique at its best. Although the material has appeared

previously in recent surgical publications, the convenience of this compilation enhances its usefulness. As Dr. Lahey points out, the standardization of an operative procedure and the familiarity with that procedure brought about by constant practice are invaluable in reducing mortality. Those of us who have had the opportunity of witnessing the superb operative surgery performed by Dr. Lahey and his staff can attest to the success of his theory. The reader who is interested in the surgical treatment of diseases of the thyroid and gastro-intestinal tract will find full details of Dr. Lahey's methods and vast experience. The reviewer was surprised, however, to find little or no reference to the use of sulfanilamide and related compounds as adjuncts to surgery.

E. S. S.

In Search of Complications. An Autobiography by EUGENE DE SAVITSCH, M.D. 396 pp. $3.00. *Simon and Schuster, New York, 1940.*

One is not surprised at a juvenile result when an individual under forty decides his life deserves an autobiography.

W. H. M.

The Retina. By S. L. POLYAK. 607 pp. Illus. $10.00. *University of Chicago Press, Chicago, 1941.*

This treatise is a valuable contribution to scholarship and research. The scope is remarkable. The author gives us a brief discussion of comparative anatomy and physiology, then swings into a discussion of laboratory technics. Some of this material is commonplace to the expert, but it is useful for those whose experience is limited, and serves to emphasize properly experimental technic. The treatment of the minute anatomy of the retina is necessarily laborious and detailed, but the reading is facilitated by cross references in the text. This material, much of which represents the author's contributions, is presented with keen awareness of functional implications. An extensive bibliography, probably the most complete ever assembled, and useful illustrations are valuable items. The reader's interest is attracted to the historical account of the study of vision which is one of the chief ornaments of the book. Although somewhat verbose at times, this book is a living testament of man's quest for understanding and a monument to the dignity of patient labor.

W. H. M.

What Price Alcohol? By ROBERT S. CARROLL. 362 pp. $3.00. *The Macmillan Company, New York, 1941.*

In this book Dr. Carroll places unusual emphasis upon the individual's hereditary nervous equipment as a factor in causing alcoholism. Dissipated parents, he asserts, are especially likely to transfer defective nervous systems to their offspring, and it is from the offspring thus equipped with nervous systems which cannot withstand the stresses and strains of modern life that alcoholics are mainly drawn.

Dr. Carroll's opinions and feelings are the result of years and years of experience with patients with alcoholic problems. With this in mind Dr. Carroll devotes the larger part of his efforts to proving what is already quite obvious—the unfortunate consequences that may follow from the uncontrolled use of alcohol, and devotes a great deal of space to emphasizing the evils and dangers that may result from drinking.

Otherwise Dr. Carroll's book is chatty, loquacious and at times repetitious. To me the most interesting aspect of this book is the presentation of the feelings of a man who has devoted his entire life to the treatment of and the attempt to help individuals with this problem.

R. V. S.

Abdominal Surgery of Infancy and Childhood. By WILLIAM E. LADD and ROBERT E. GROSS. 455 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

This book, which represents the accumulated experience of Doctors Ladd and Gross, contains a fund of information of immense importance to surgeons, pediatricians, and general practitioners. The clarity and conciseness of the writing are matched by the excellence of the illustrations. The scope and quality of the senior author's understanding of his field result in part, no doubt, from his life-long and undivided attention to that field, and constitute a formidable argument in favor of the specialization of surgical practice. Accompanying the text are tables entitled "Results of Treatment," a valuable feature that the reviewer would like to see more frequently in other surgical publications.

E. S. S.

Sinus. By RUSSELL CLARK GROVE. 165 pp. Illus. $2.00. *Alfred A. Knopf, New York, 1941.*

Although Doctor Grove does not mention it in this very informative book, one of the outstanding symptoms of sinus disease is an inordinate curiosity as to the nature and causes of what is popularly called "sinus." To allay this curiosity, the author, through his clear and logical statements of fact, has performed a far-reaching service. It is to be hoped that those who read this book will be induced thereby to seek out competent medical and surgical treatment, instead of continuing ineffective home remedies, or what is infinitely worse, "under-done" treatments by incompetent physicians who hold themselves to be specialists in this field.

Doctor Grove explains to the layman that "sinus" refers to a cavity in the bones of the face, and not to a disease; that all human beings have eight sinuses, which are divided into four pairs, all different in size, shape and name; and that these sinuses when healthy have certain useful physiological functions.

After explaining the anatomy of the sinuses, their functions, the types of sinus disease, their symptoms and their effects on the human body, the two final chapters of the book are devoted to the treatment of sinus disease. There is no attempt to instruct the patient how to treat himself, but Doctor Grove recounts the forms

of treatment now in use, as well as those formerly used. Nose drops and solutions, short-wave therapy, diathermy, x-rays, and irrigation of the antrum by puncturing, are all discussed. Doctor Grove disputes the rather popular notion that puncturing an antrum will result in worse sinus disease; that, once performed, it will have to be repeated over and over again. "If the procedure is carried out properly," Doctor Grove says, "there is no justification for such a belief."

The final question as to whether or not surgery is worthwhile in the treatment of sinus disease is answered emphatically in the affirmative. This point of view will comfort many sufferers pondering the advisability of a surgical operation. Doctor Grove lets it be known that he is aware of the advice, heard almost daily, "never to let a nose and throat doctor touch your sinuses; if you do, you'll have trouble the rest of your life." He calls this a misconception and gives numerous reasons why bad operative results are seen. Patients who are perfectly well following operations are seldom mentioned; only the others are heard from. Moreover, unless an operation is full and complete, it can only be ineffectual. Much sinus surgery is "under-done," *i.e.*, not completed. Today's tendency, Doctor Grove explains, is to perform fewer operations, but to operate thoroughly.

L. M. P.

Diseases Affecting the Vulva. By ELIZABETH HUNT. 215 pp. Illus. $4.00. *C. V. Mosby Company, St. Louis, 1940.*

Any contribution to our knowledge of the diseases affecting the membranes of the vulva and lower internal genitalia is worthwhile. This monograph, while failing to cover the subject adequately, is worthy of note. There are many excellent colored illustrations, and colored photographic reproductions of variations of the common, and a few of the uncommon, diseases of the skin as they affect the vulva. But the subject matter lacks much of the information desired on many of these diseases. The bibliography is good but not complete.

The author confuses her American readers by referring to most of the medicinal agents by the proprietary British names. In numerous instances the treatment advised for specific conditions has been radically modified, or changed completely in recent years, and the author fails to note these changes or merely mentions them without thorough discussion.

Despite numerous faults the work is a valuable contribution to gynecological and dermatological literature, and may be recommended to the student or practitioner.

J. H. L.

Diseases of Women. By HARRY STURGEON CROSSEN and ROBERT JAMES CROSSEN. 9th ed. 948 pp. $12.50. *C. V. Mosby Company, 1941.*

This edition of one of the most used text books on gynecology has been extensively revised to include the most recent advances in the field. The bibliography has been brought up to date.

The most valuable addition has been the inclusion of extensive reviews of the voluminous recent literature on the physiology of the reproductive tract, with special emphasis on the rôle of the glands of internal secretion. Not only are the theoretical points stressed, but the conservative and practical, clinical applications are discussed in some detail.

The sections on pathology are good and have been revised to include the most recent additions to our knowledge on ovarian tumors.

The chapter on inflammatory conditions fails to stress the importance of chemotherapy. While there is a brief review of the literature, the authors display little evidence of experience with the new potent chemotherapeutic agents.

As it has been for years, this book continues to be one of the outstanding text books and minor reference works on gynecology.

J. H. L.

Cardiac Clinics. A Mayo Clinic Monograph. By FREDRICK A. WILLIUS. 276 pp. Illus. $4.00. *C. V. Mosby Company, St. Louis, 1941.*

In the Foreword, the author explains that the subject matter of this little volume was compiled from informal discussions in the Proceedings of the Staff Meetings of the Mayo Clinic. Fourteen chapters are included, in which the discussion is built largely about actual cases, often reinforced by necropsy. Such subjects as Diseases of the Pericardium, Rheumatic Heart Disease, Bacterial Endocarditis, Cardiovascular Syphilis; Hypertensive, Thyroid and Congenital Heart Disease; Coronary Disease, Functional States and Disturbances of Cardiac Rhythm are discussed in an easy style in excellent English. Such material is held together by remarks on Signs and Symptoms, Treatment and Management, Historic Excerpts and Miscellaneous Topics. The reader must not expect to find a complete text-book of cardiovascular disorders, but, within its scope, the book is remarkably informing and salient. The author might profit by directing his attention to the statement that diastolic murmurs are "always important" (p. 18), while to and fro murmurs of cardio-respiratory origin are well described (p. 28); this apparent contradiction could be clarified readily. Perhaps the small heart of certain types of concretio cordis should be discussed more fully, to offset the descriptions of cardiac hypertrophy associated with pericardial adhesions. The author should be congratulated on his description of digitalis delirium, a sadly neglected subject.

J. T. K.

Diseases of the Foot. By EMIL D. W. HAUSER. 472 pp. Illus. $6.00. *W. B. Saunders Company, Philadelphia & London, 1939.*

There has been a definite tendency to consider affections of the foot as either of minor significance, unworthy of much study, or of sufficiently serious character to demand the attention of a specialist. As a result, the general practitioner has neglected his responsibility toward such affections. One factor leading to this

attitude has been the difficulty of obtaining a satisfactory compendium on foot ailments, since most of the material has been distributed among special journals or in large tomes.

Hauser's book serves to correct this difficulty. It presents in a direct manner a comprehensive description of the affections of the foot. After a useful survey of the anatomical, embryological, and physiological factors of importance, the author describes the methods of examination of the foot and the principles of care for normal feet. Pathological conditions are then presented. The diseases are grouped at times etiologically and at other times anatomically but they are so arranged that it is quite simple to locate the disease under consideration. The factors leading to the disease, the clinical picture, and the methods of treatment are simply and concisely presented. The book thus fills a definite need in a most satisfactory manner.

I. W. N.

Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. A Lecture Syllabus. By J. L. GAMBLE. [105 pp.], Diagrams. *Department of Pediatrics, The Harvard Medical School, 1941.*

This is the "third printing," really the third, enlarged edition of a syllabus that Dr. Gamble prepared for his own students. Having been discovered by students in other schools this brochure has become very popular,—justly so.

In forty-six charts Dr. Gamble has depicted the distribution of electrolytes and water in body fluids and the shifts that occur in normal and abnormal processes. Accompanying each chart is its description and a brief discussion of the facts that deserve special emphasis. Both the charts and the text reveal the author's skill as an expositor. Necessarily the reader must have been drilled in the physico-chemical principles that are involved. Having a good working knowledge of these he will be led quickly and efficiently to an appreciation of matters that are of very great clinical importance—led better, I believe, than by any other text of similar scope.

The brochure is attractively printed and bound by Spaulding Moss Co.

This is a syllabus to be amplified by lectures. The resulting brevity has left a few passages obscure and occasionally a plain statement open to debate. Thus, a lecturer might well emphasize the limitations casually referred to by the word *usually* in the following passage: "The diagnosis of acidosis or alkalosis can usually be made with sufficient definition for clinical purposes by the measurement of the 'total CO_2' of plasma." Reference to the simple equilibrium equation for the carbonic acid-bicarbonate system shows three variables. To evaluate any one the other two must be determined, although Nature is often trusted to reduce the requirements to one. Also, in view of the above, the retention of the words *acidosis* and *alkalosis* is comparable to retaining only *up* and *down* for movement in space of three dimensions. Thus the author, having committed himself directly and by implication to two different definitions of acidosis, finds it necessary in his description of chart 13 to reverse the usual significance of increased bicarbonate.

In short he has abandoned simplicity at the behest of an outworn tradition. It is like stretching *up* to serve for *north* and *west*.

It is noteworthy that Gamble has used a form of diagram which leads him away from certain other archaic expressions still used by biochemists and to depictions pleasing to a physical chemist. One could wish that he had employed exclusively in his text the straight-forward expressions implied in his diagrams. He declares: "we have to deal not with salts but with separately controlled quantities of individual ions," yet, having made this plain both by diagram and text, his text specifies *molecules*, such as NaCl, $NaHCO_3$, etc., for the existence of which there is no evidence. *Base* is used in the sense peculiar to biochemistry when it is plainly evident that cation is meant. Round-about expressions that follow the long abandoned approach to the colligative properties of solutions by way of "osmotic pressure" are true to the confusing habit of the biochemist. Several such infelicities are fully compensated by the clarity of the diagrams. Nor will they seriously disturb anyone who is trained never to revere words but to seek the intent of their use.

Since the syllabus was written for students, it must be judged in large part by its effects on students. Awakening is illustrated by one student who, evidently flabbergasted by having discovered in this text that ions are clinically important, wrote on his examination that the theory of electrolytic dissociation was originated by Gamble. Appreciation by the more intelligent majority was expressed by another student's exclamation: "Thank God for Gamble!"

W. M. C.

BOOKS RECEIVED FOR REVIEW

Workmen's Compensation and the Physician. By HENRY H. JORDAN. 180 pp. $3.00. *Oxford University Press, New York, 1941.*

Subacute Bacterial Endocarditis. By EMANUEL LIBMAN and CHARLES K. FRIEDBERG. 108 pp. Illus. $2.75. *Oxford University Press, New York, 1941.*

Arthritis in Modern Practice. By OTTO STEINBROCKER. 606 pp. Illus. $8.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

The Value of Health to a City. Two Lectures Delivered in 1873. By MAX VON PETTENKOFER. Translated from the German, with an Introduction by HENRY E. SIGERIST. 52 pp. $1.00. *The Johns Hopkins Press, Baltimore, 1941.*

Behind the Mask of Medicine. By MILES ATKINSON. 348 pp. $3.00. *Charles Scribner's Sons, New York, 1941.*

Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. A Lecture Syllabus. By J. L. GAMBLE. 105 pp. Diagrams. *Department of Pediatrics, The Harvard Medical School, 1941.*

Psychoanalytical Method and the Doctrine of Freud. By ROLAND DALBIEZ. In 2 vols. Translated from the French by T. F. Lindsay. Volume 1. Exposition, 415 pp. Volume 2. Discussion, 331 pp. $9.00. *Longmans, Green and Co., London [etc.], 1941.*

Immunology. By NOBLE PIERCE SHERWOOD. 2nd ed. 639 pp. Illus. $6.50. *C. V. Mosby Company, St. Louis, 1941.*

Toxemias of Pregnancy. By WILLIAM J. DIECKMANN. 521 pp. Illus. $7.50. *C. V. Mosby Company, St. Louis, 1941.*

Surgical Practice of the Lahey Clinic. 897 pp. Illus. $10.00. *W. B. Saunders Company, Philadelphia and London, 1941.*

Medical Clinics of North America. Volume 25, Number 6. Military Medicine. 418 pp. Illus. Paper, $12.00, Cloth, $16.00 per Clinic Year. *W. B. Saunders Company, Philadelphia and London, November, 1941.*

Synopsis of Allergy. By HARRY L. ALEXANDER. 246 pp. Illus. $3.00. *C. V. Mosby Company, St. Louis, 1941.*

Synopsis of Genitourinary Diseases. By AUSTIN I. DODSON. 3rd ed. 302 pp. Illus. $3.50. *C. V. Mosby Company, St. Louis, 1941.*

Hippocratic Medicine. Its Spirit and Method. By WILLIAM ARTHUR HEIDEL. 149 pp. $2.00. *Columbia University Press, New York, 1941.*

Woman's Personal Hygiene. Modern Methods and Appliances. By LEONA W. CHALMERS. 192 pp. Illus. $2.00. *Pioneer Publications, New York, 1941.*

The Blood Bank and the Technique and Therapeutics of Transfusions. By ROBERT A. KILDUFFE and MICHAEL DEBAKEY. 558 pp. Illus. $7.50. *C. V. Mosby Company, St. Louis, 1942.*

Neuroanatomy. By FRED A. METTLER. 476 pp. Illus. $7.50. *C. V. Mosby Company, St. Louis, 1942.*

The Doctors Mayo. By HELEN B. CLAPESATTLE. 822 pp. Illus. $3.75. *University of Minnesota Press, Minneapolis, 1941.*